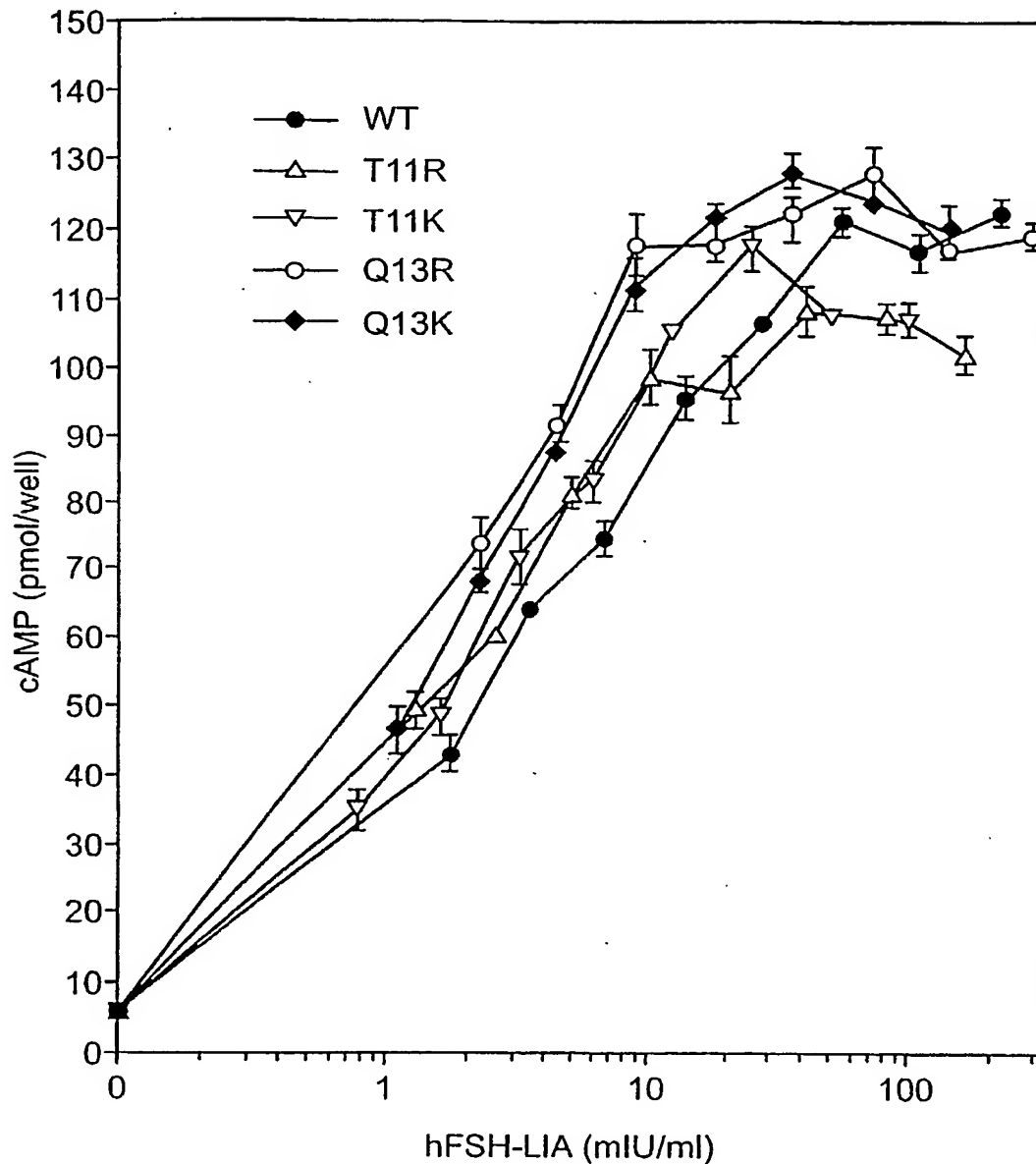


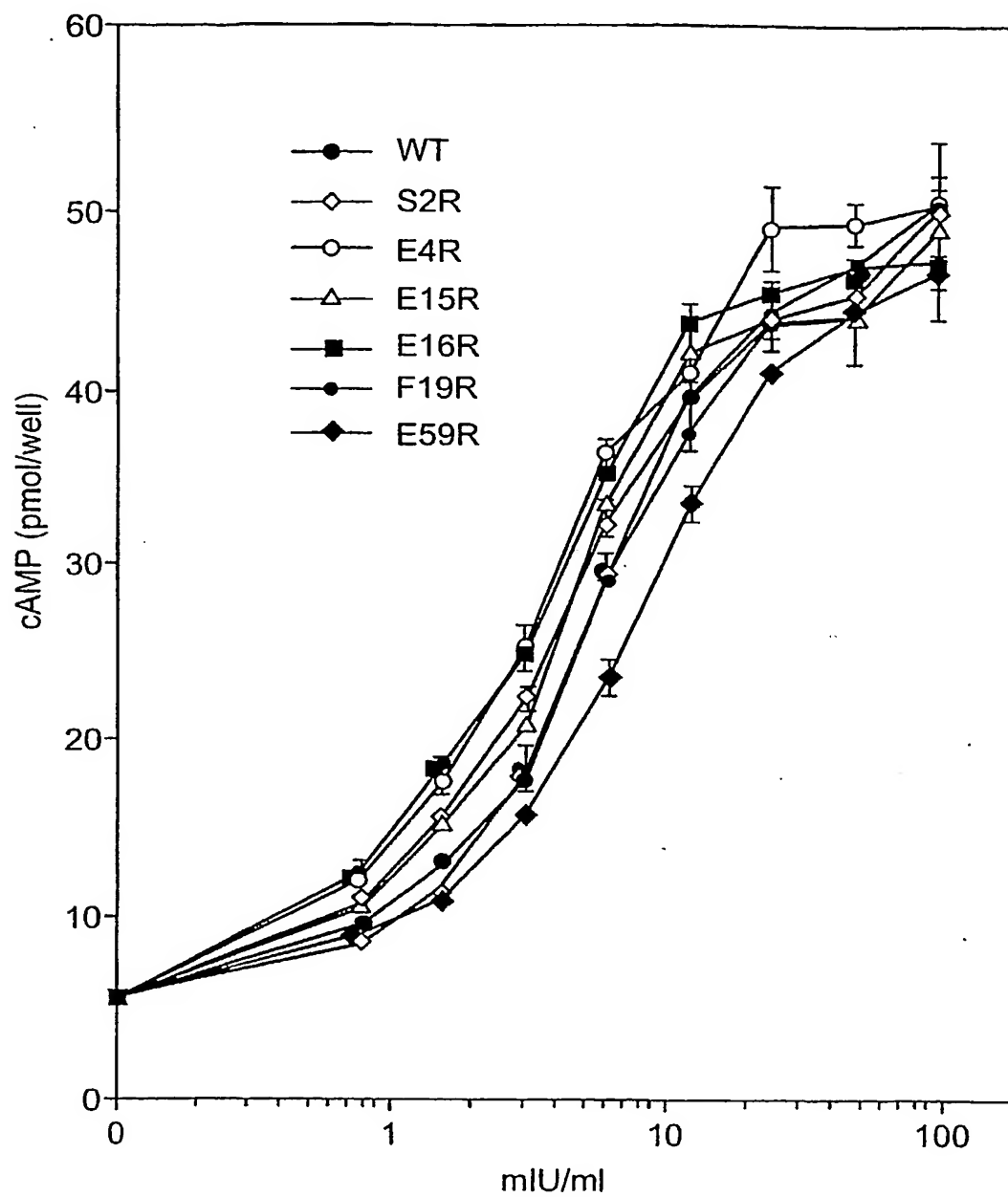
1/37

EFFECT OF SINGLE MUTATIONS ON FSH BIOACTIVITY IN VITRO
STIMULATION OF cAMP PRODUCTION
IN CHO-FSHR CELLS

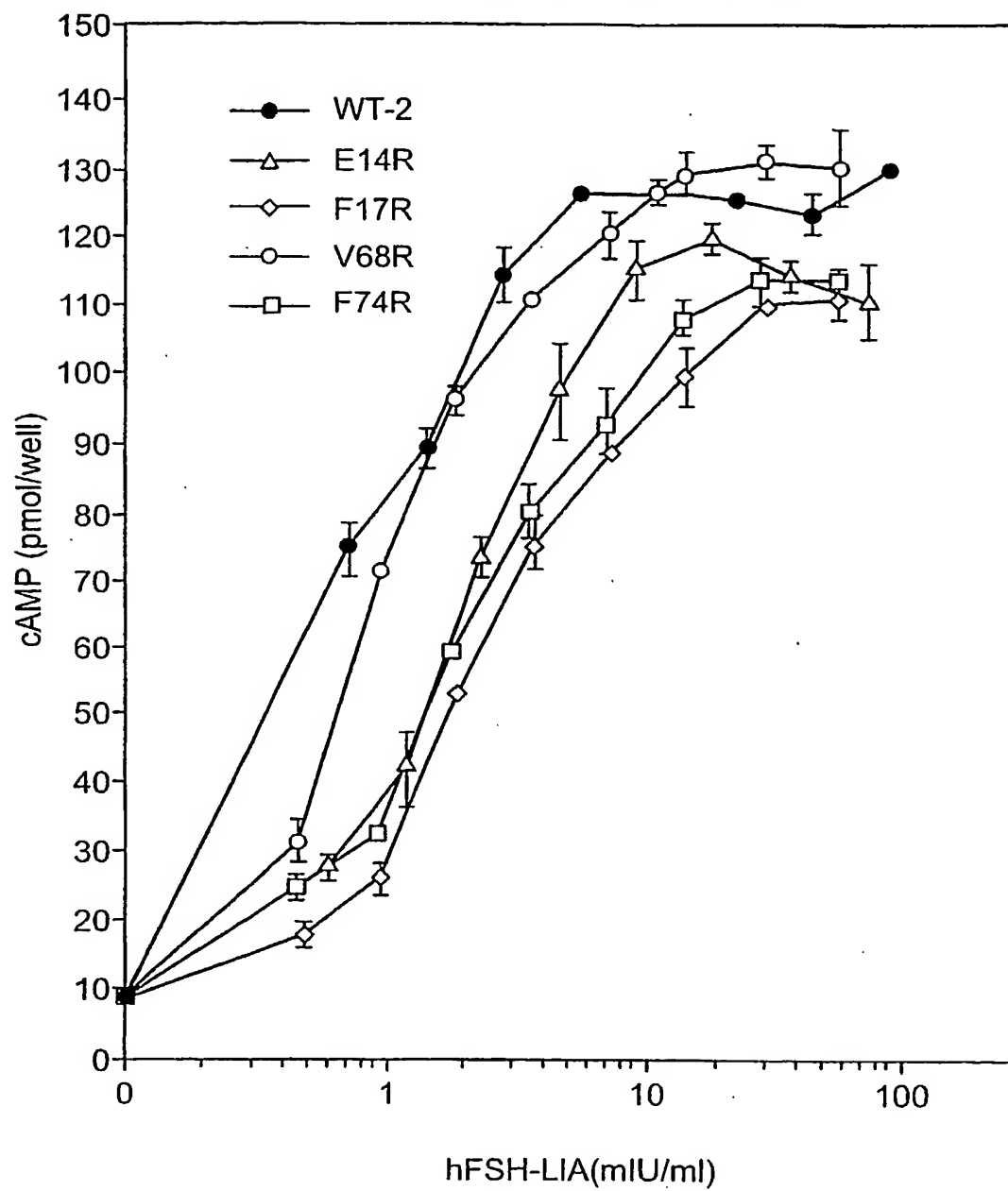
**FIG. 1A**

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EFFECT OF SINGLE MUTATIONS ON FSH BIOACTIVITY IN VITRO

**FIG. 1B**

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STIMULATION OF cAMP PRODUCTION
IN CHO-FSHR CELLS**FIG. 1C**

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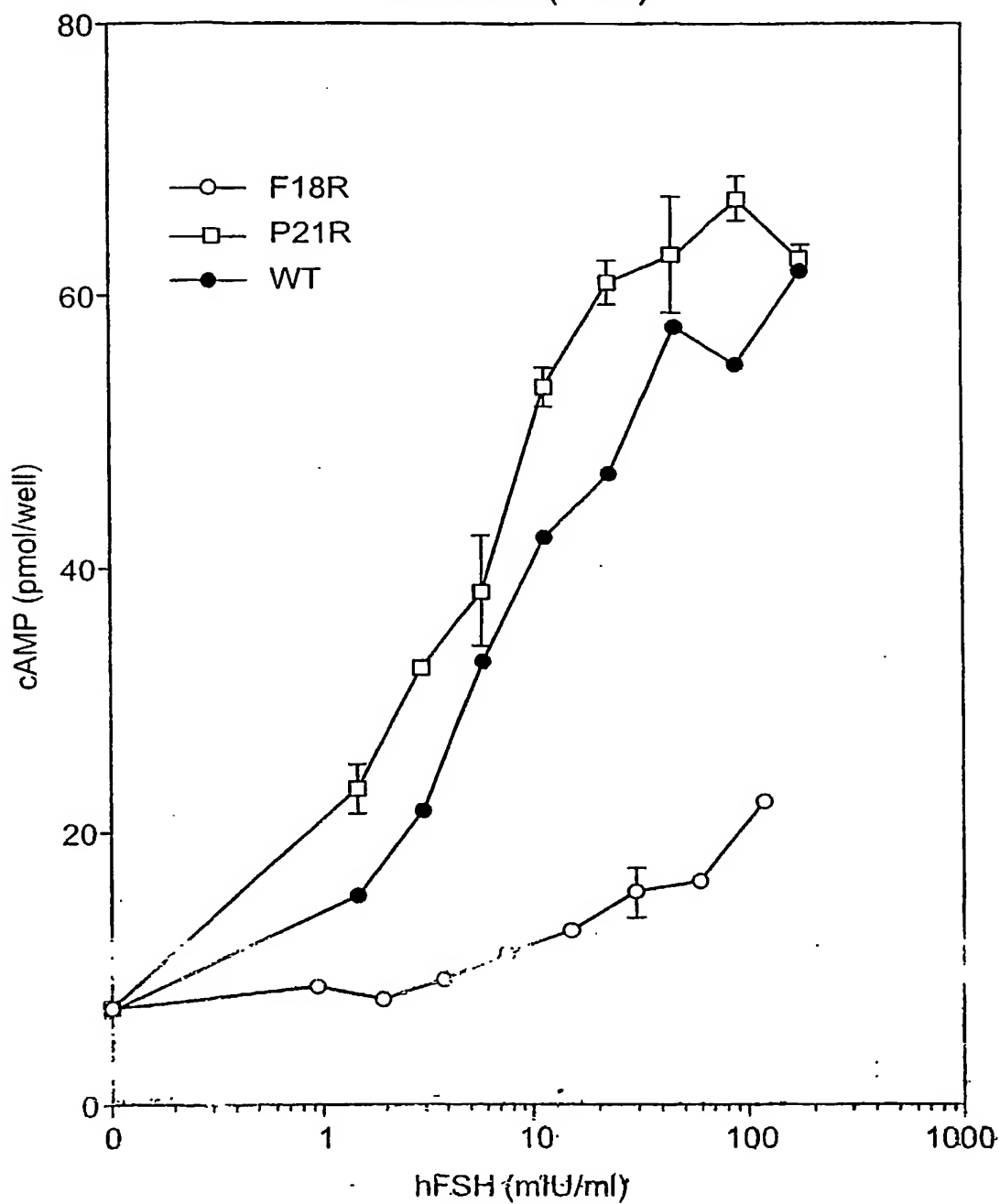
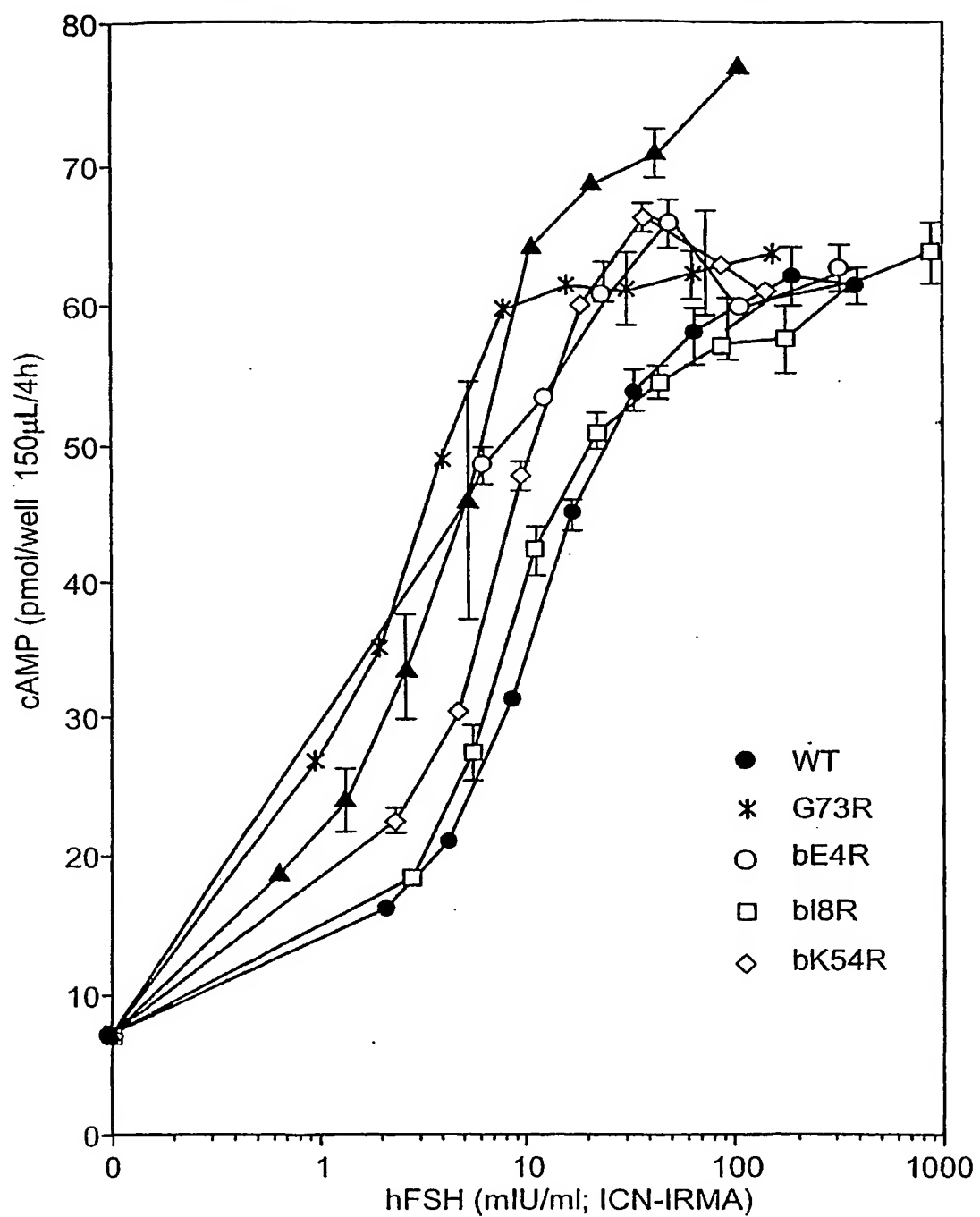
EXAMPLE OF "LOSS OF BIOACTIVITY"
MUTATION (F18R)

FIG. 1D

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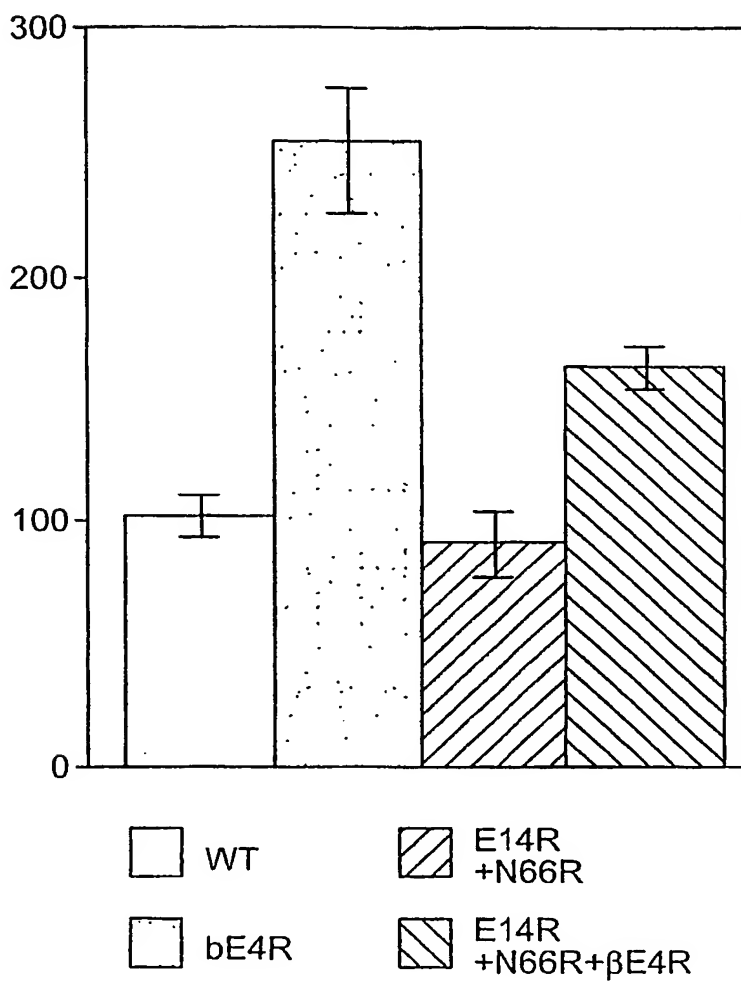
cAMP STIMULATION IN CHO-FSHR CELLS

**FIG. 1E**

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EFFECT OF β E4R MUTATION ON hFSH PRODUCTION

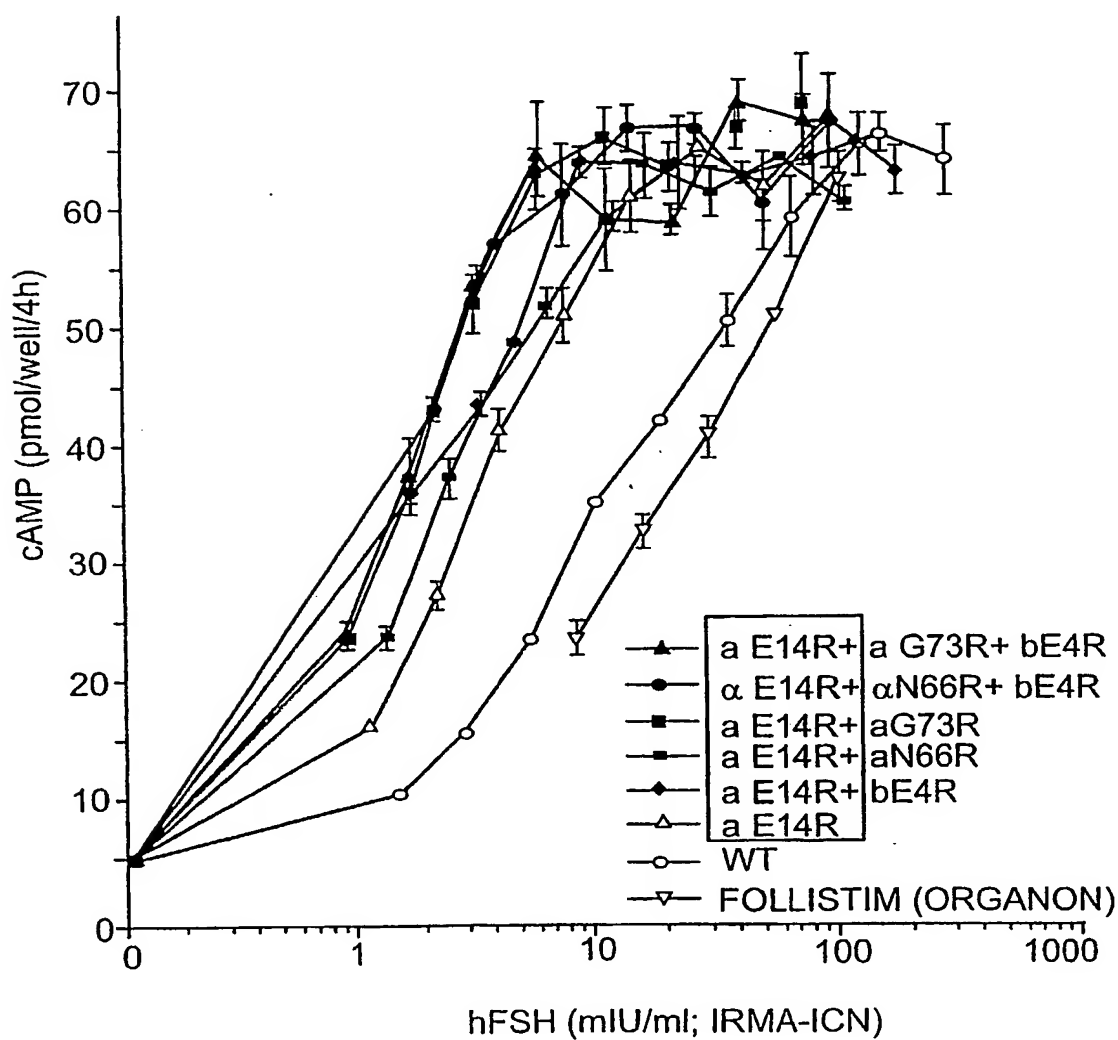
%WT
(PRODUCTION
OF NON-
MUTATED
FSH=100%)

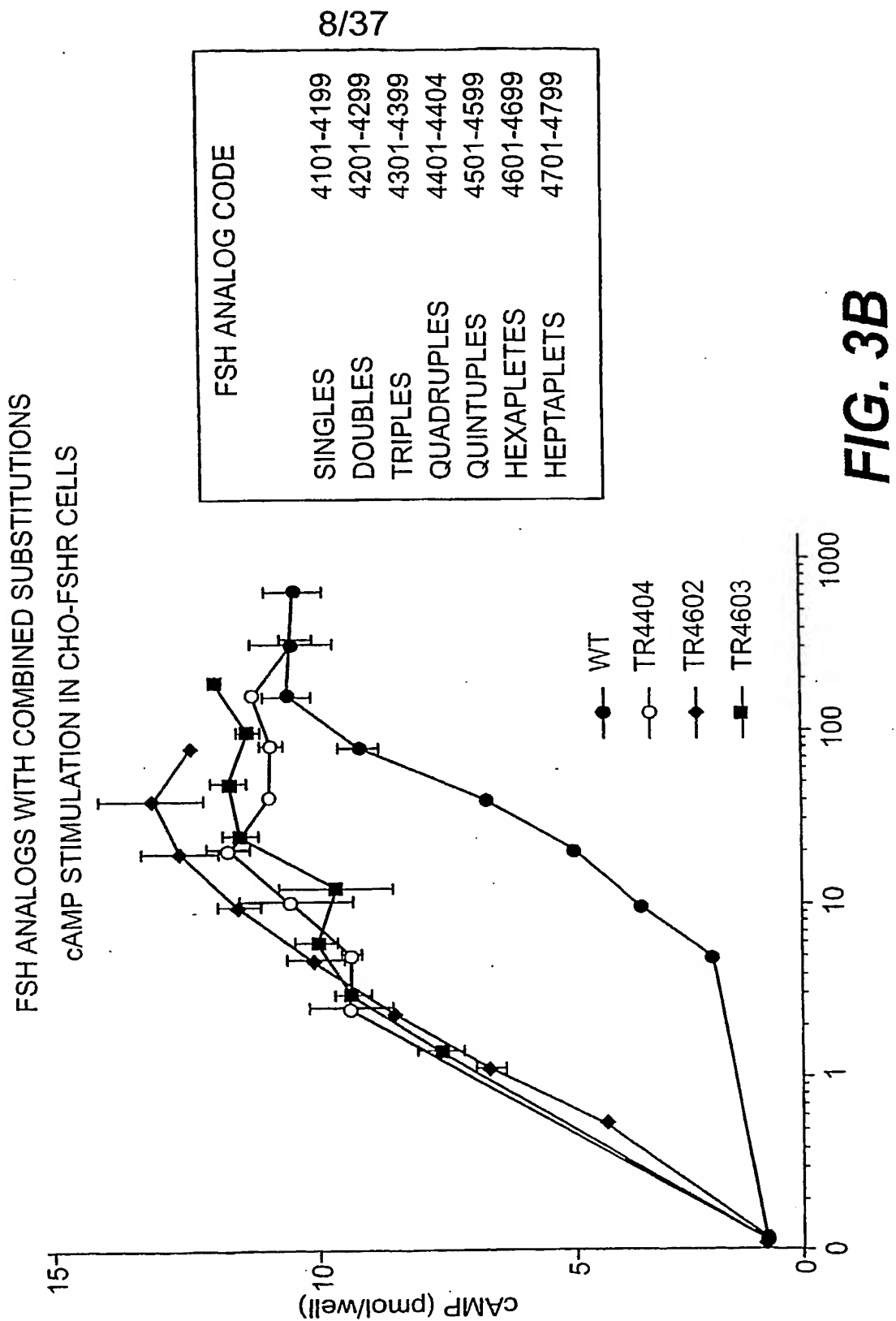
**FIG. 2**

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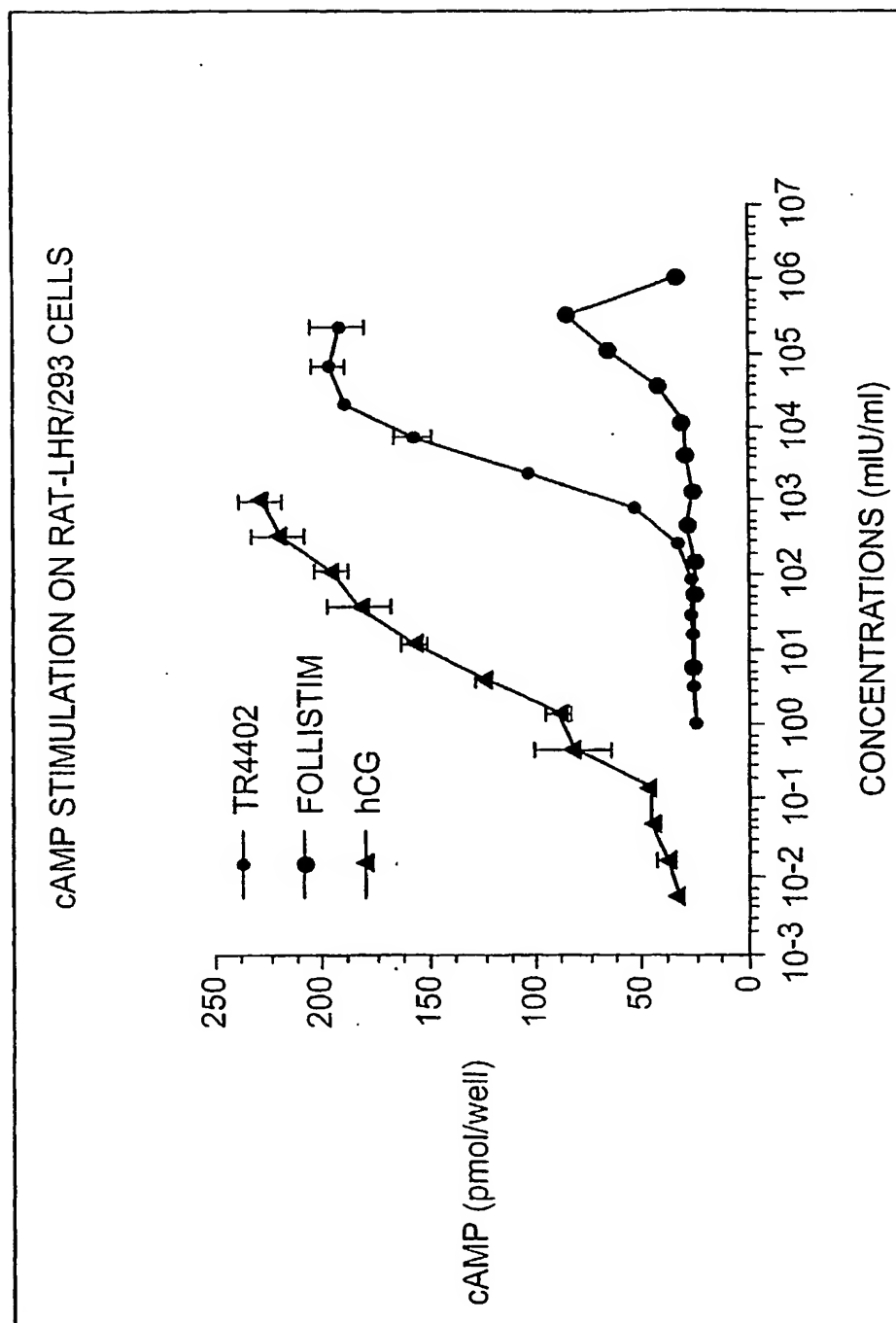
FSH ANALOGS WITH COMBINED SUBSTITUTIONS

cAMP STIMULATION IN CHO-FSHR CELLS

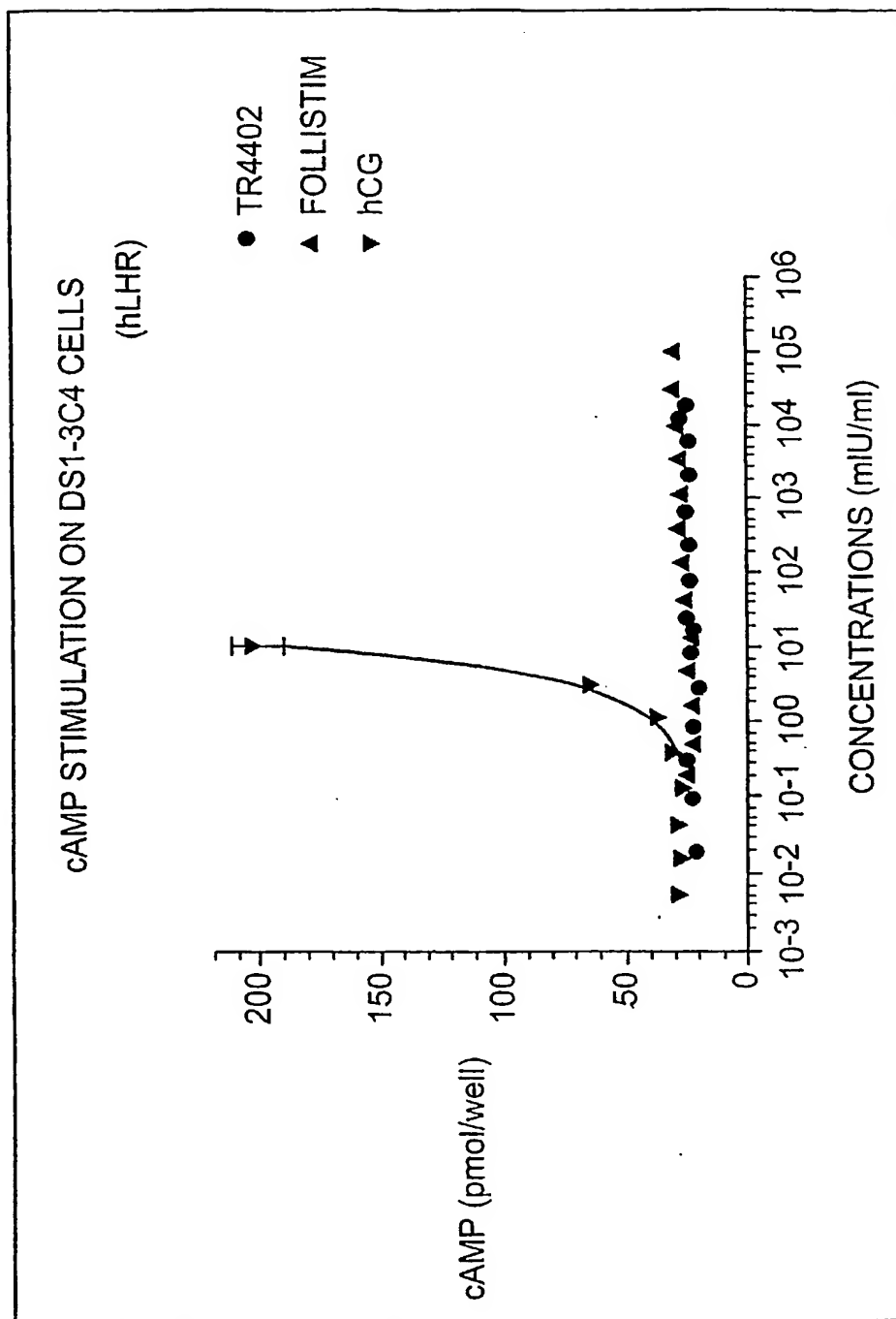
**FIG. 3A**



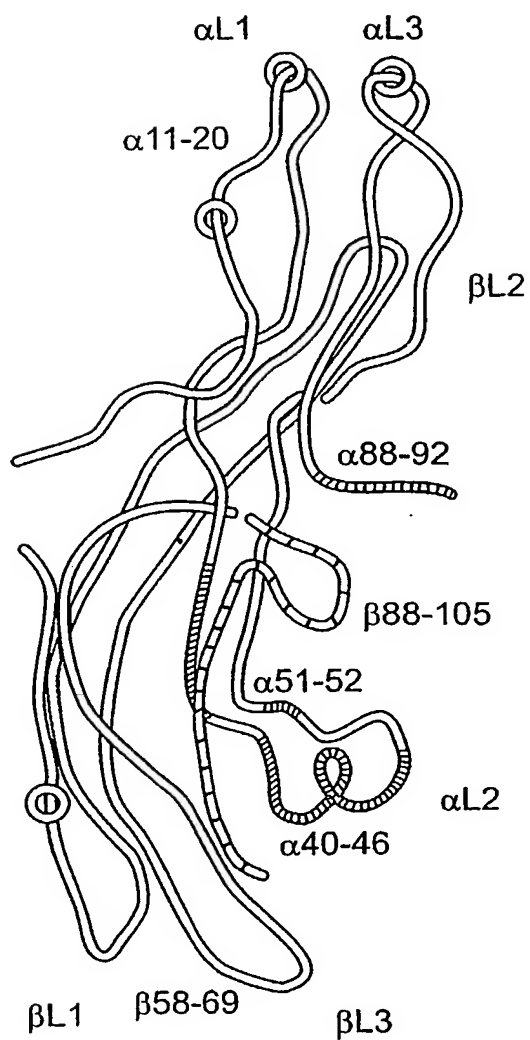
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**FIG. 4A**

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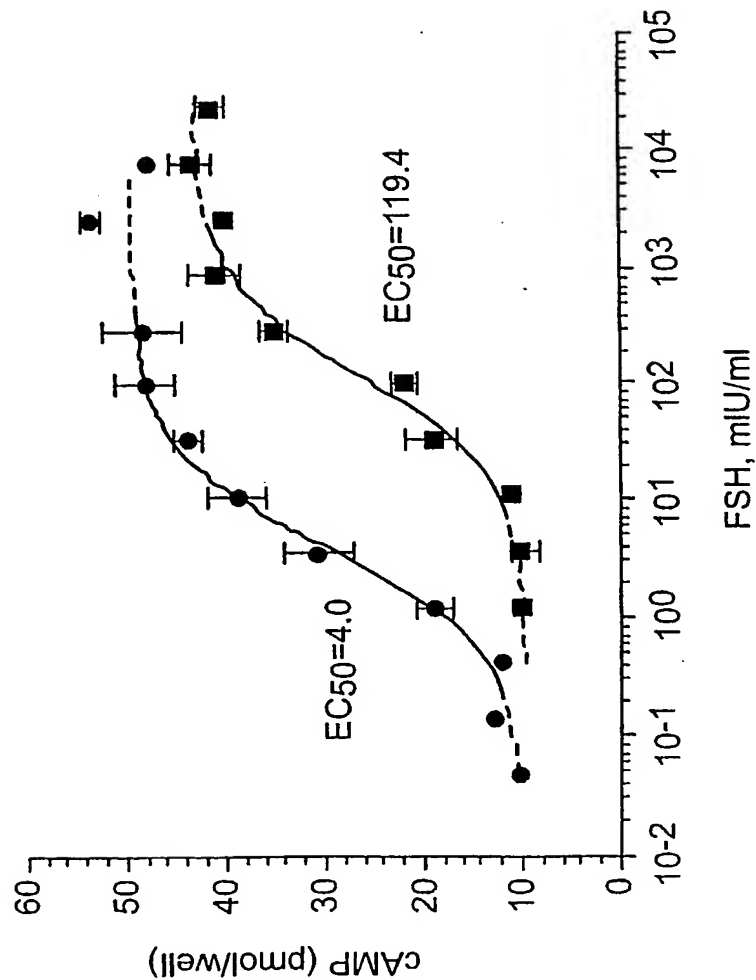
**FIG. 4B**

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**FIG. 5**

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cAMP STIMULATION ON CHO-FSHR

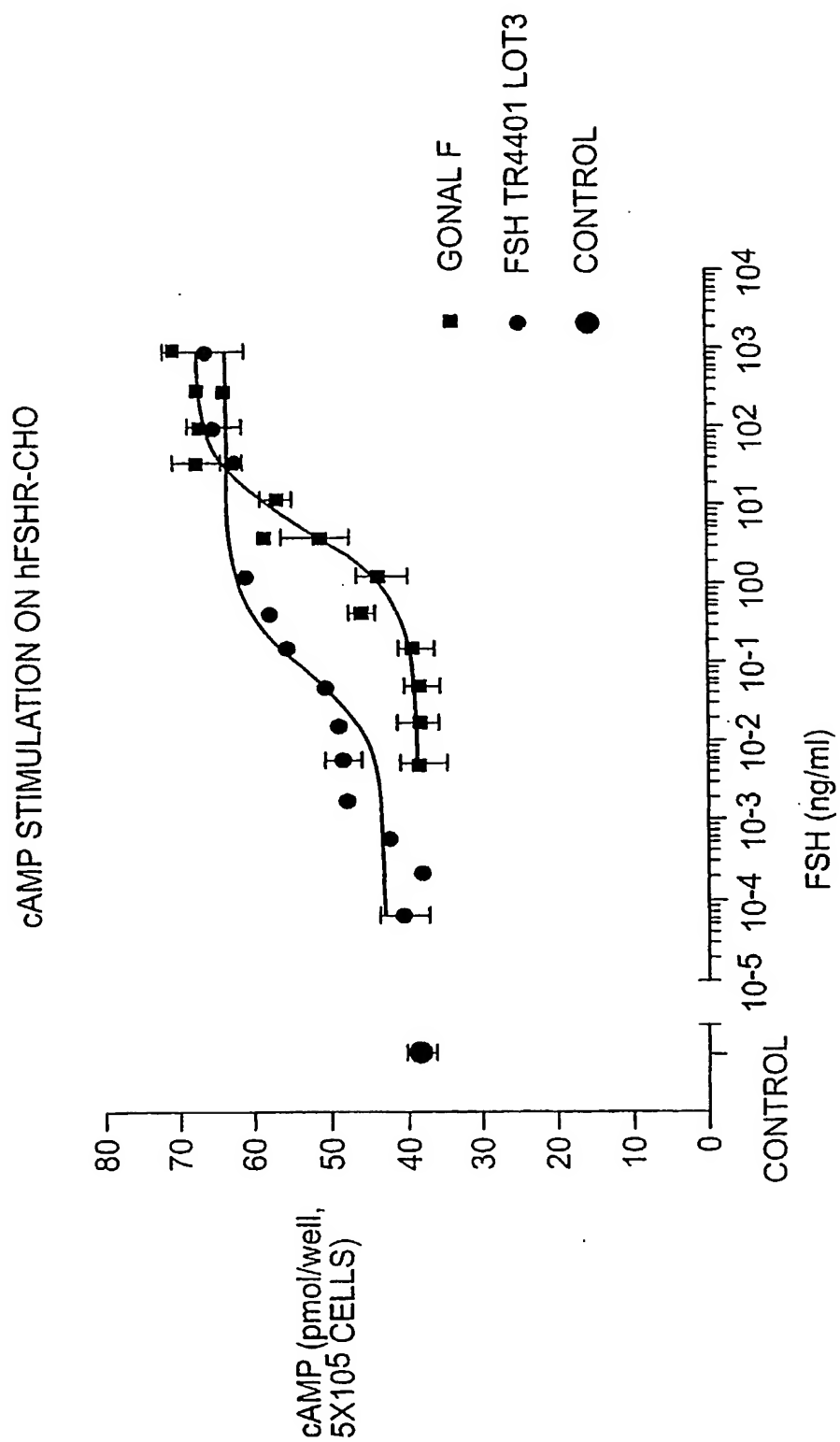


30X HIGHER POTENCY
17% HIGHER V_{MAX}

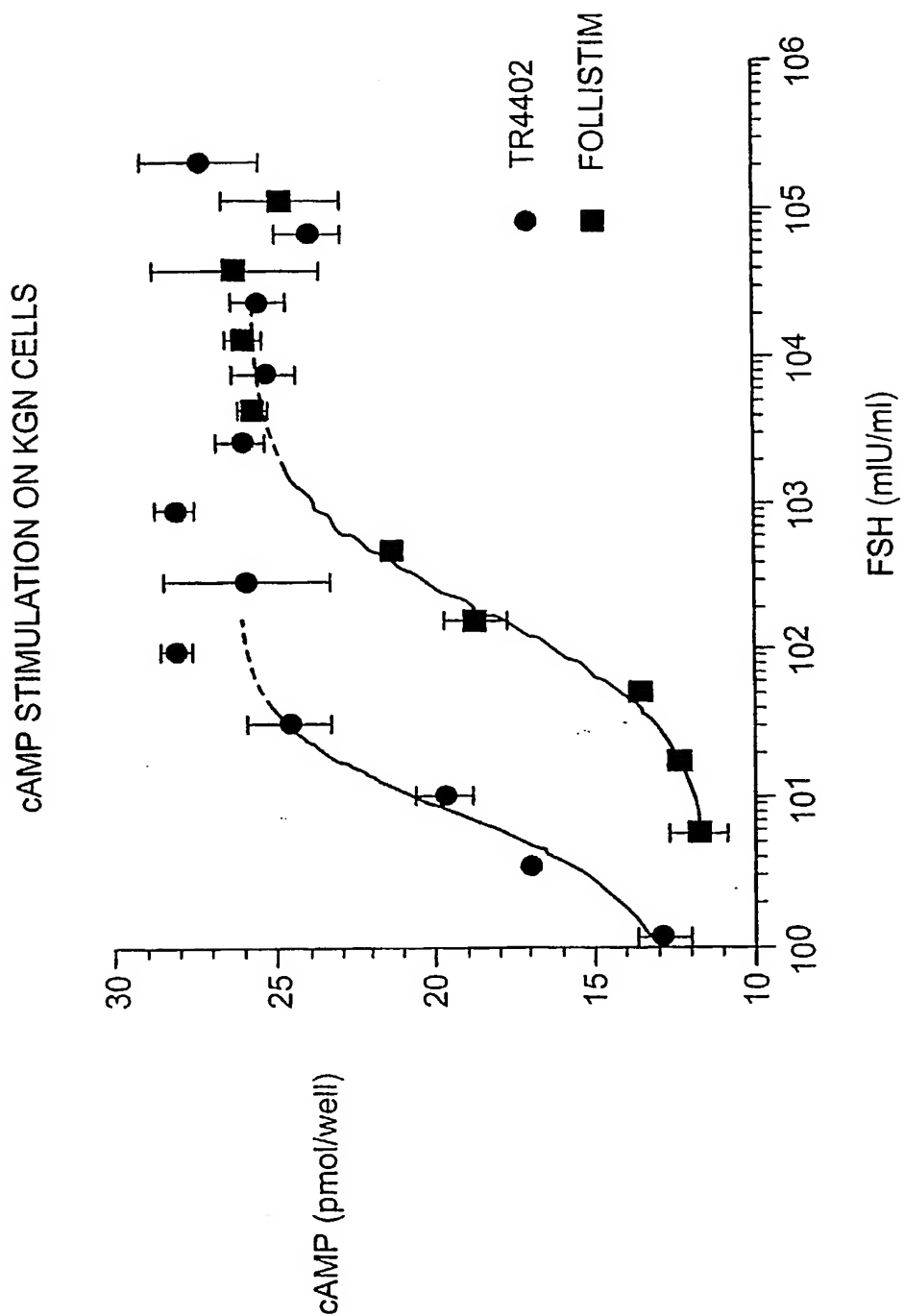
- TR4402 LOT2
- FOLLISTIM DIALYZED

FIG. 6A

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**FIG. 6B**

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**FIG. 7**

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GLHR-15 CELLS WITH LOW FSHR NUMBER

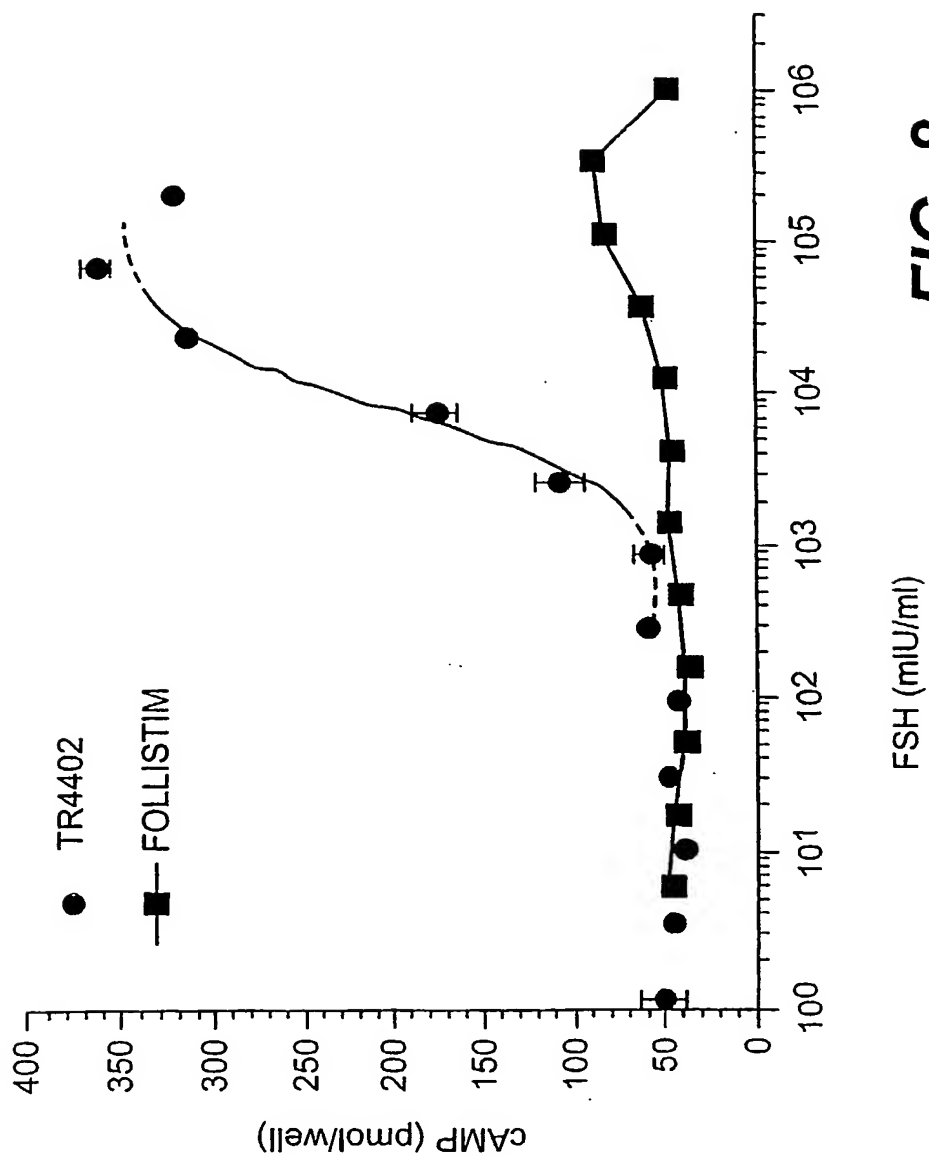


FIG. 8

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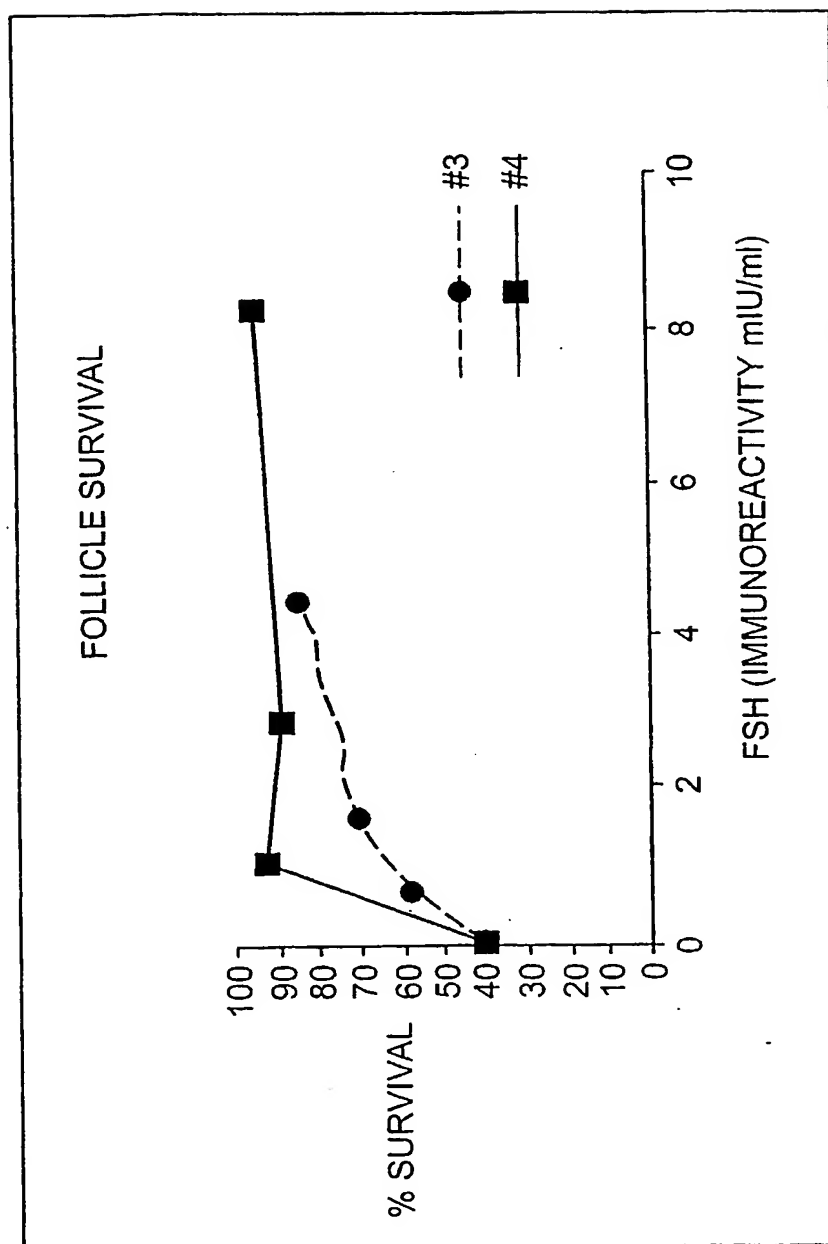


FIG. 9

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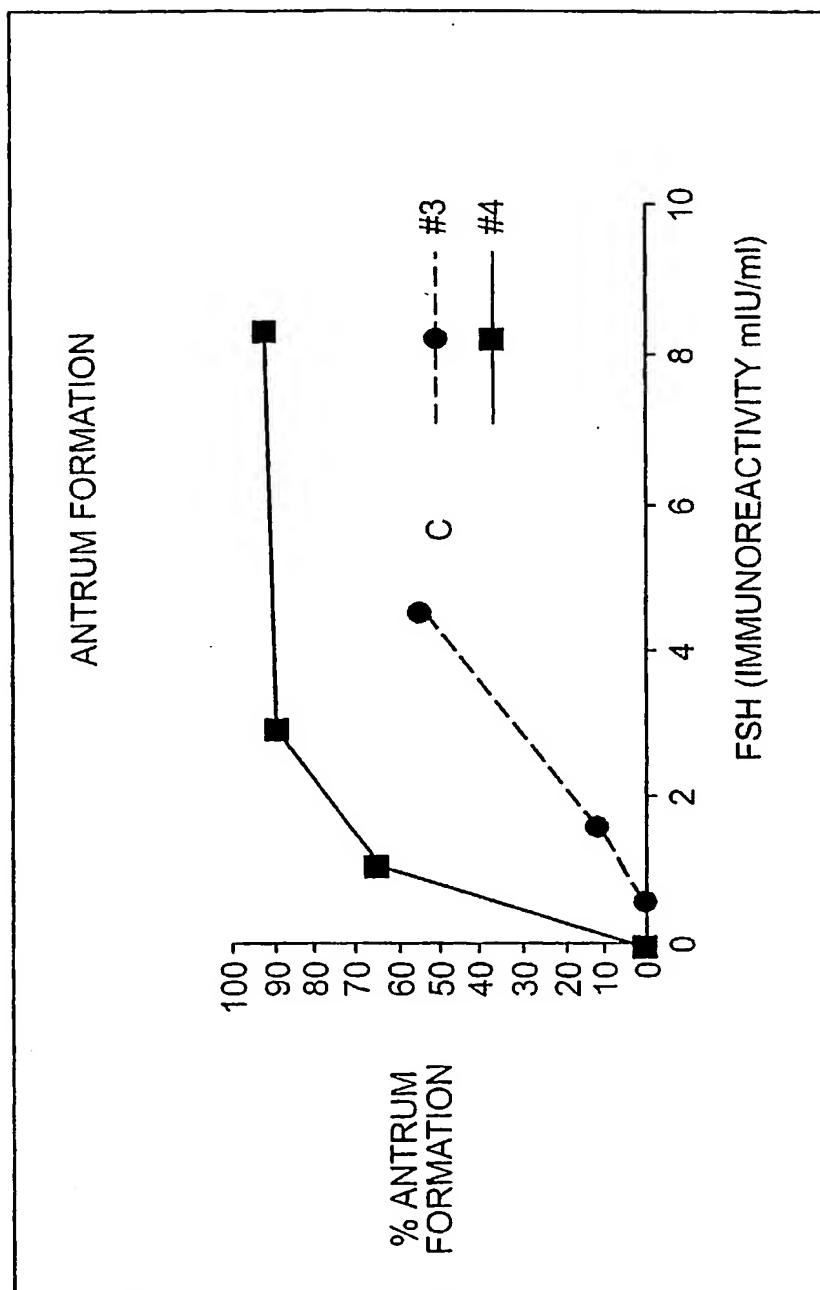
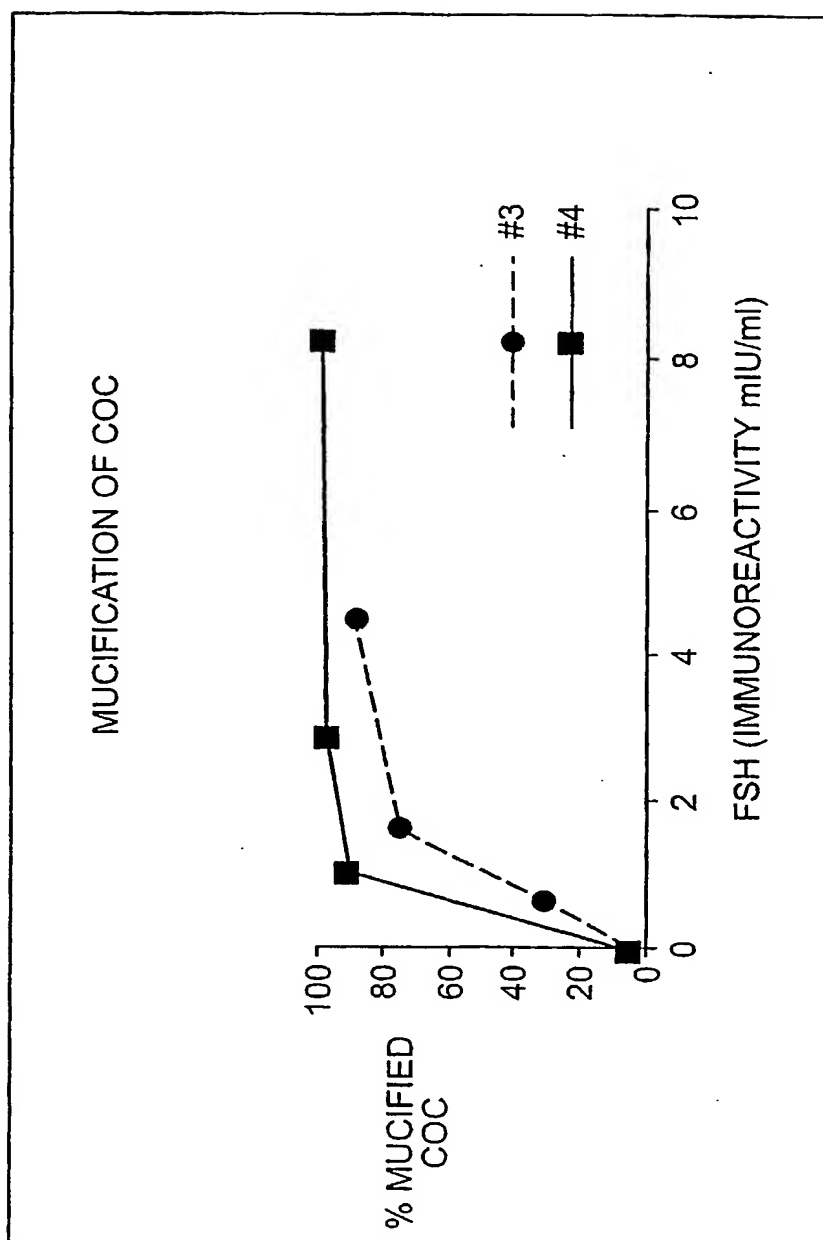


FIG. 10

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**FIG. 11A**

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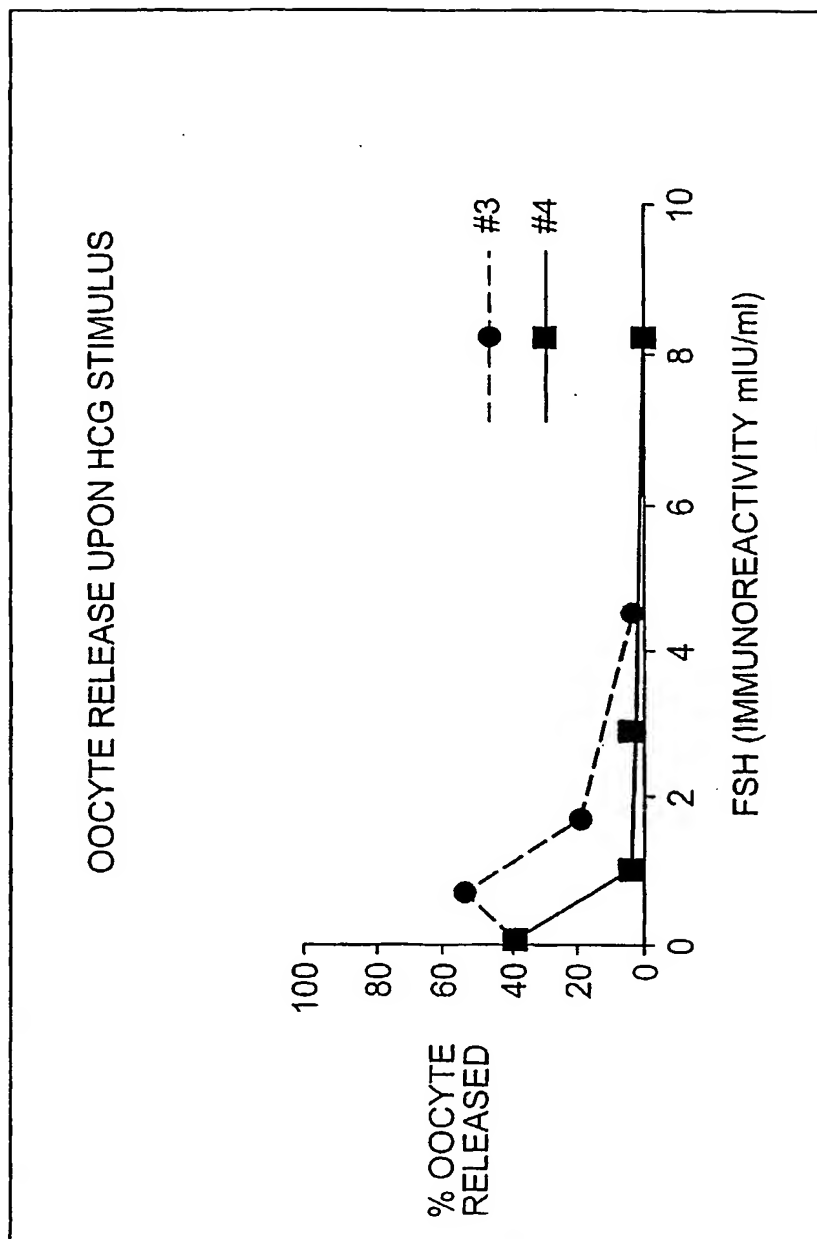
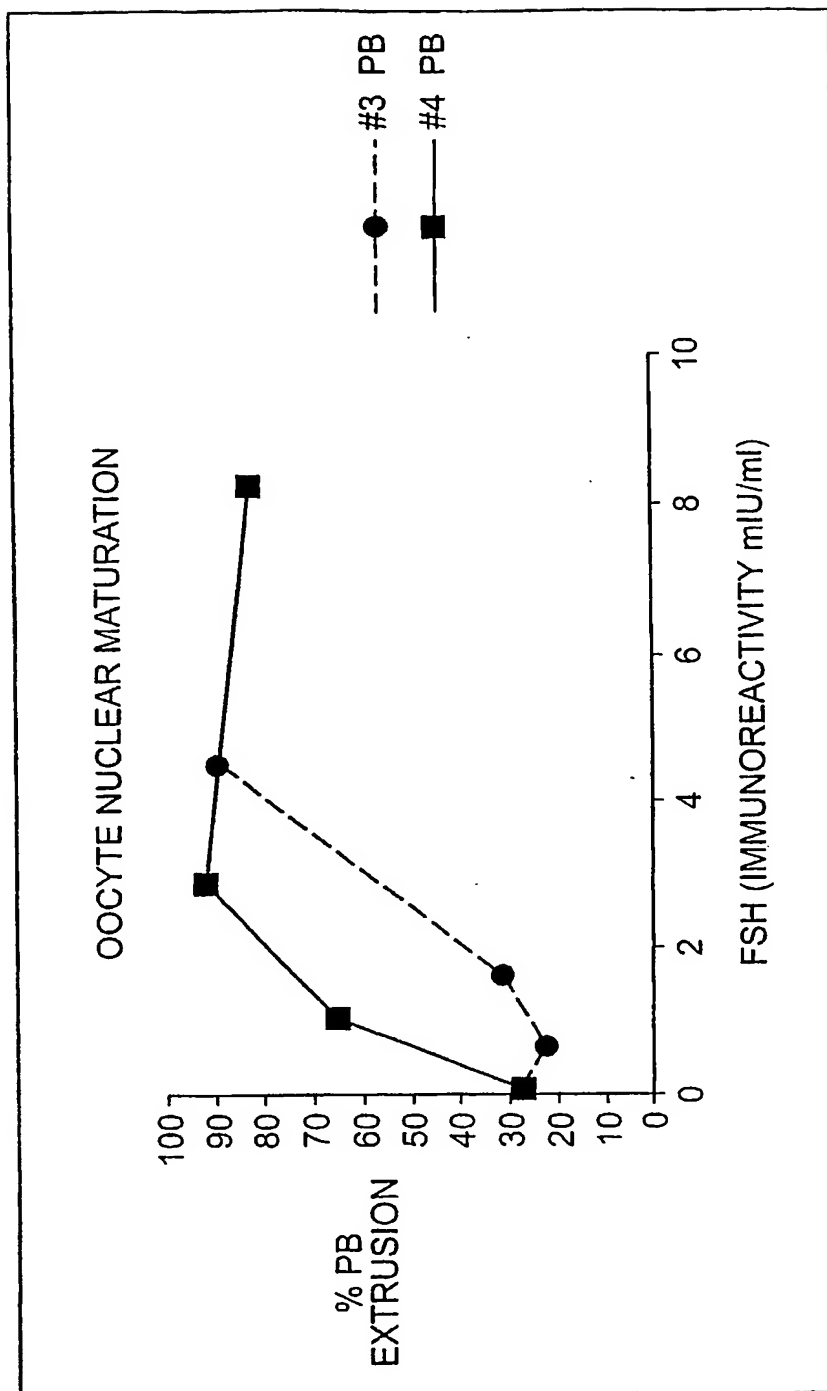


FIG. 11B

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**FIG. 12**

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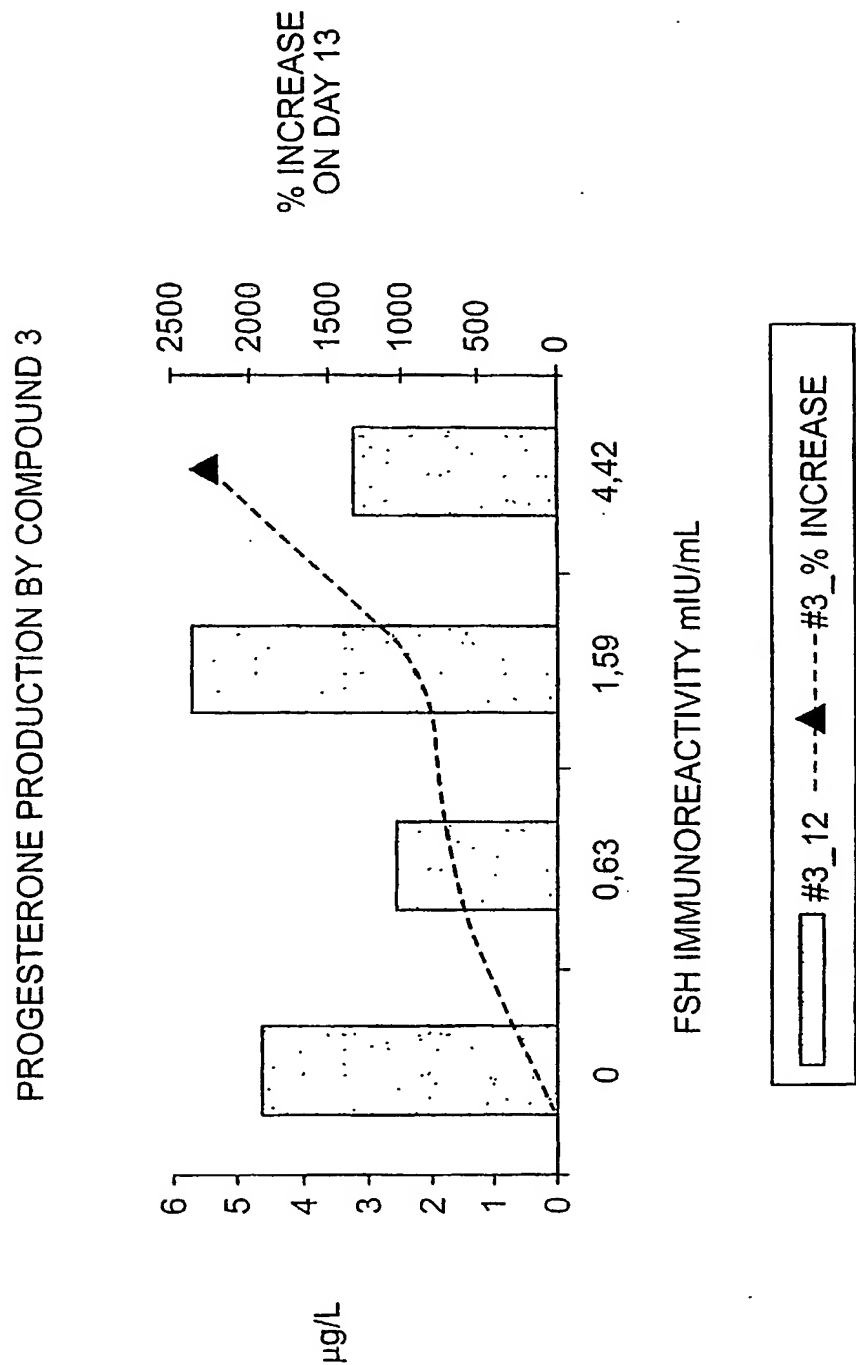


FIG. 13A

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PROGESTERONE PRODUCTION BY COMPOUND 4

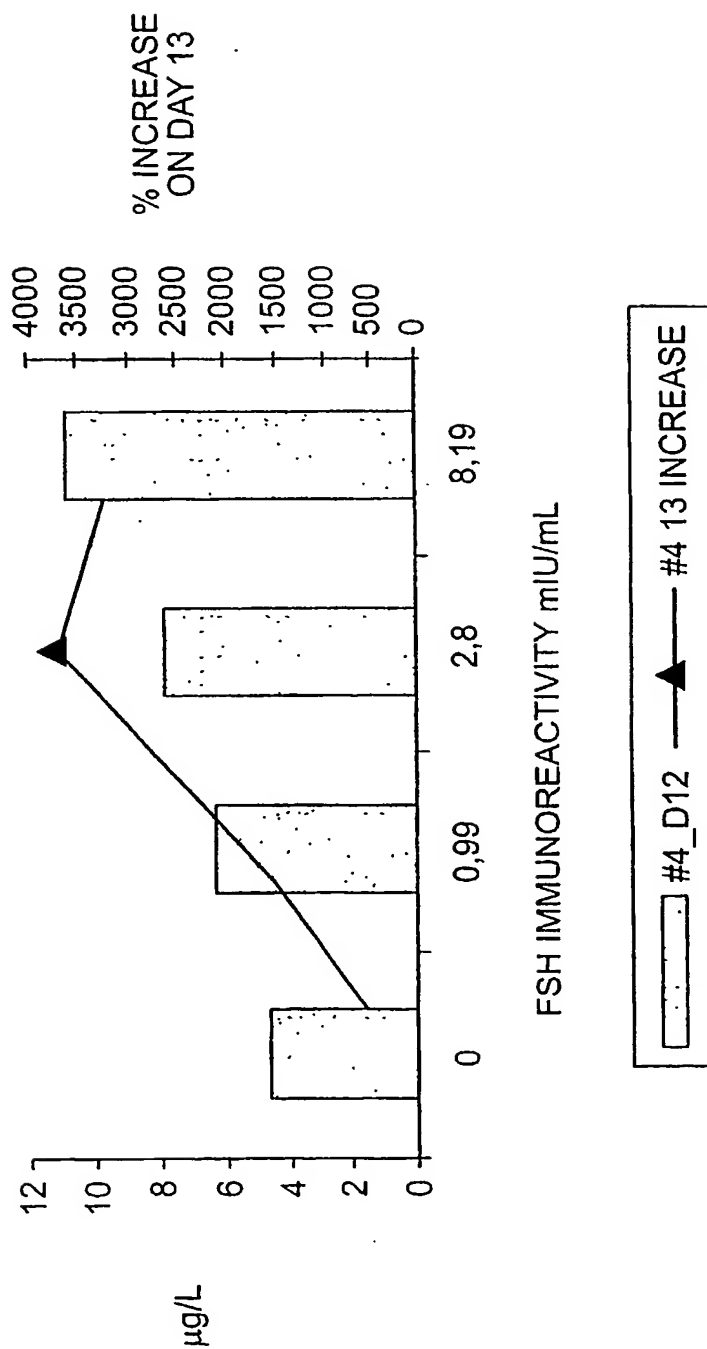
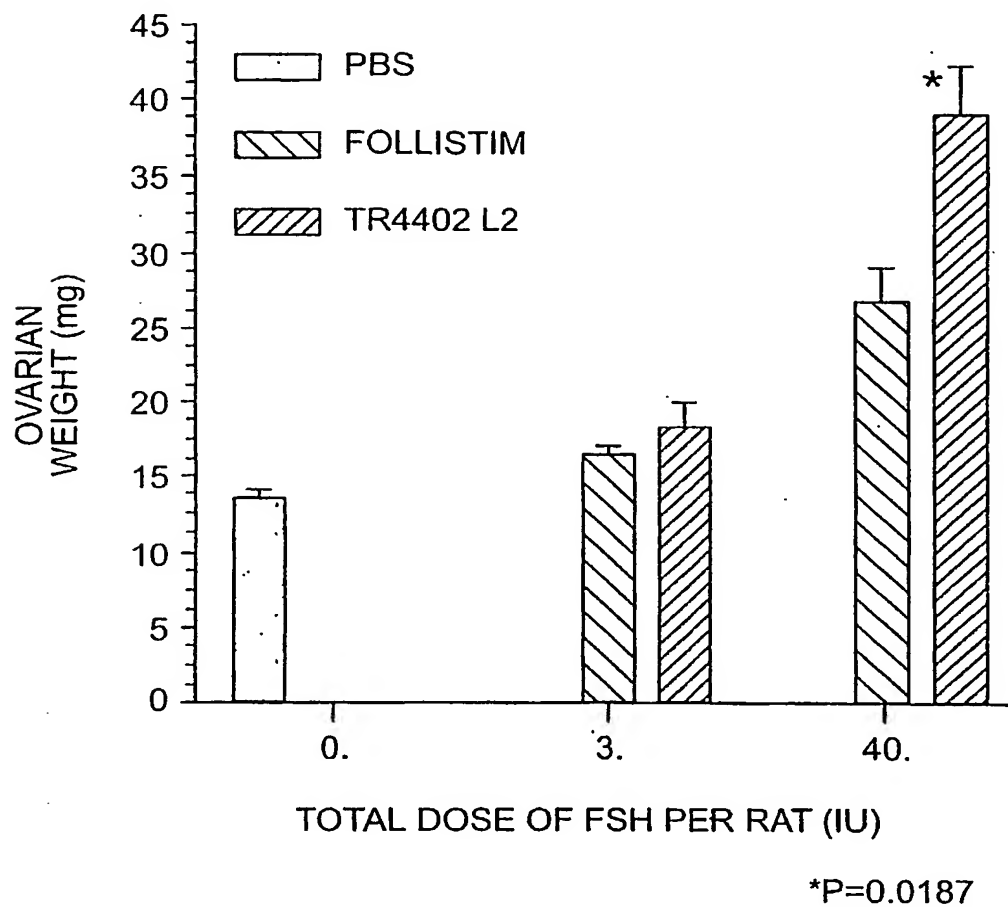


FIG. 13B

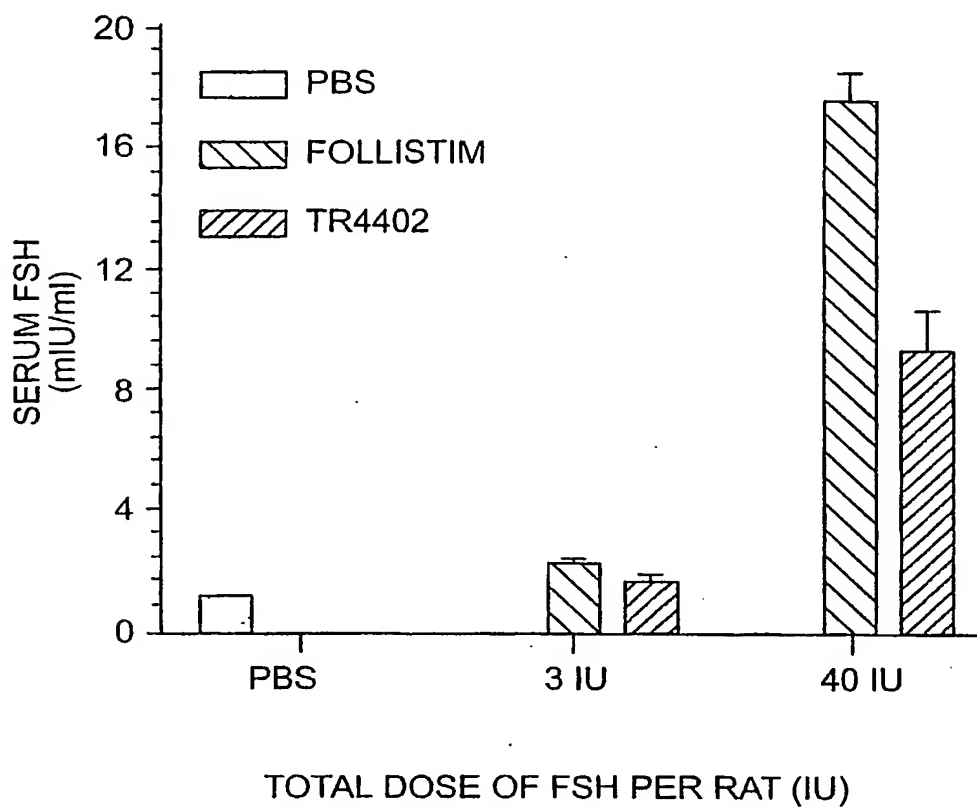
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STEELMAN-POHLEY BIOASSAY WITHOUT hCG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS**FIG. 14A**

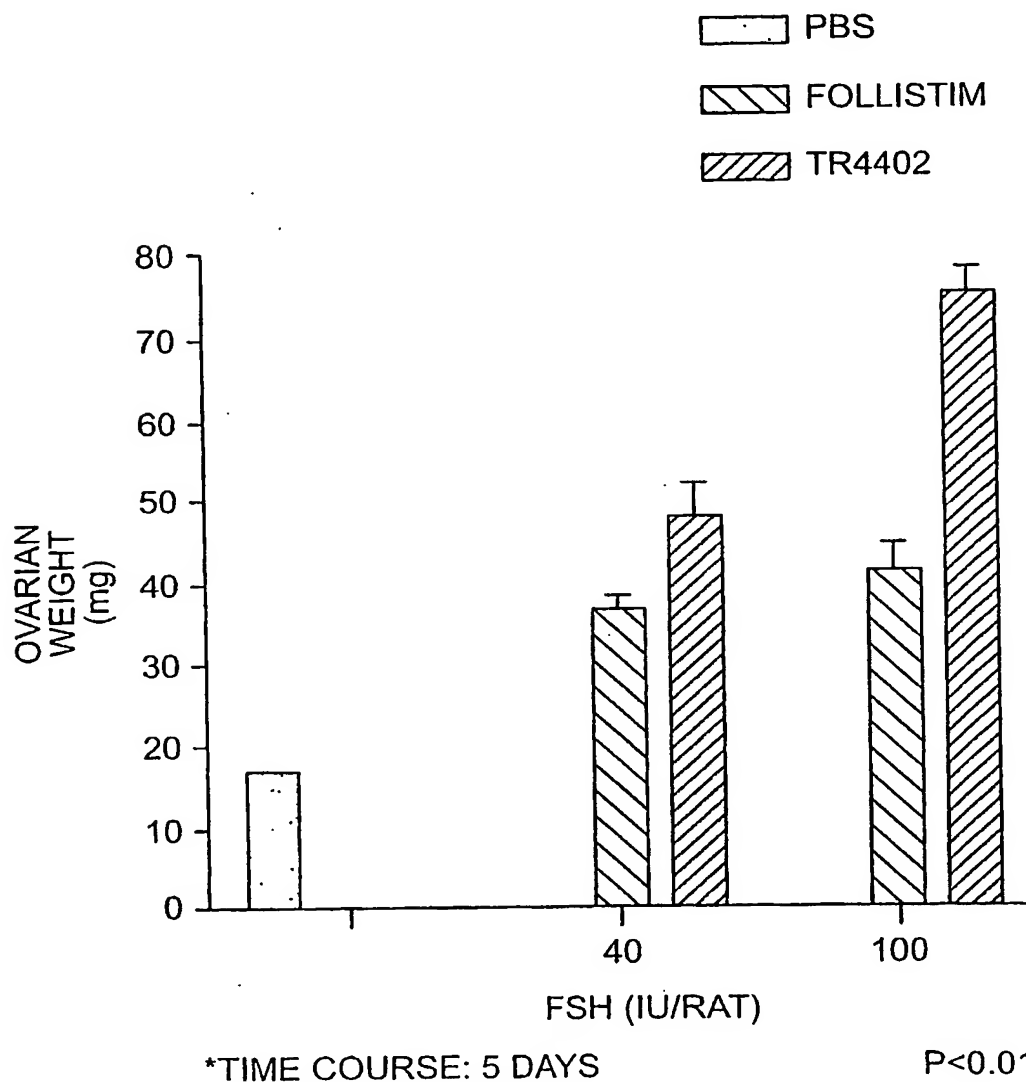
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STEELMAN-POHLEY BIOASSAY WITHOUT hVG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS

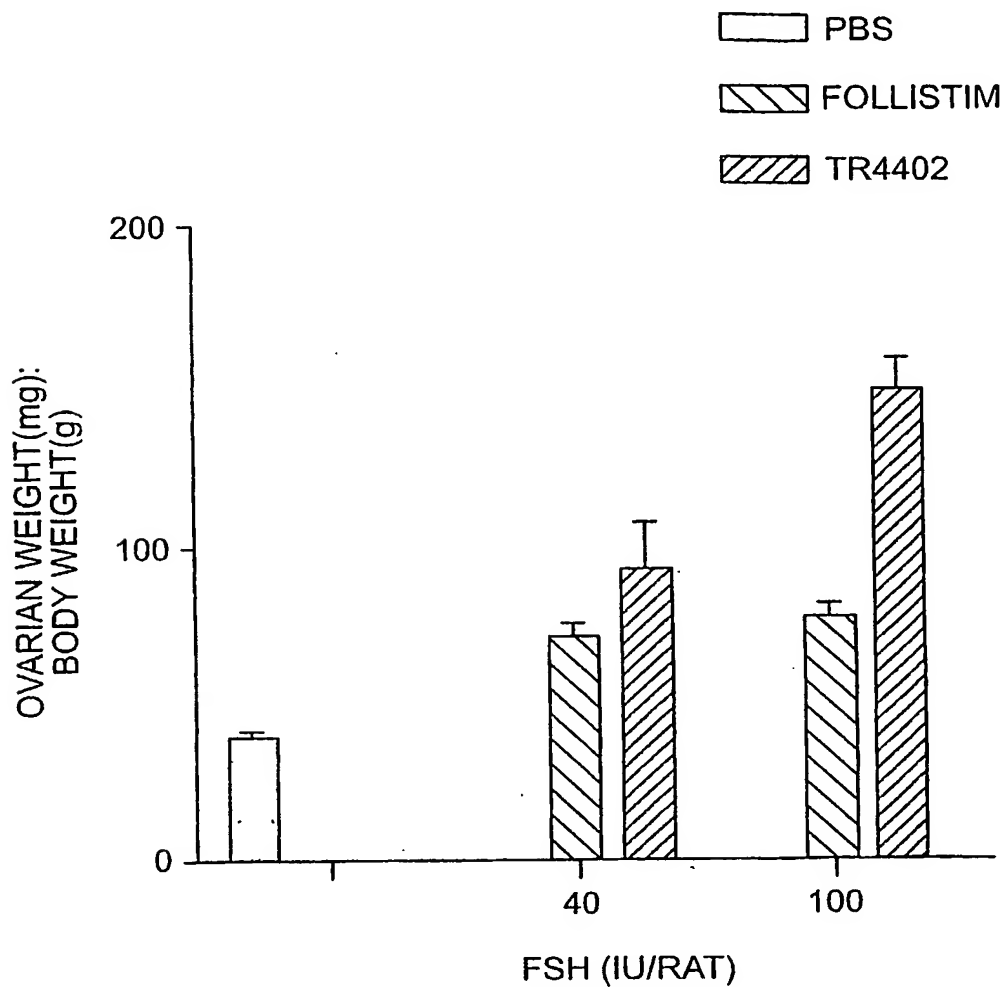
SERUM FSH LEVELS

**FIG. 14B**

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STEELMAN-POHLEY BIOASSAY WITHOUT hCG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS**FIG. 14C**

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STEELMAN-POHLEY BIOASSAY WITHOUT hCG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS

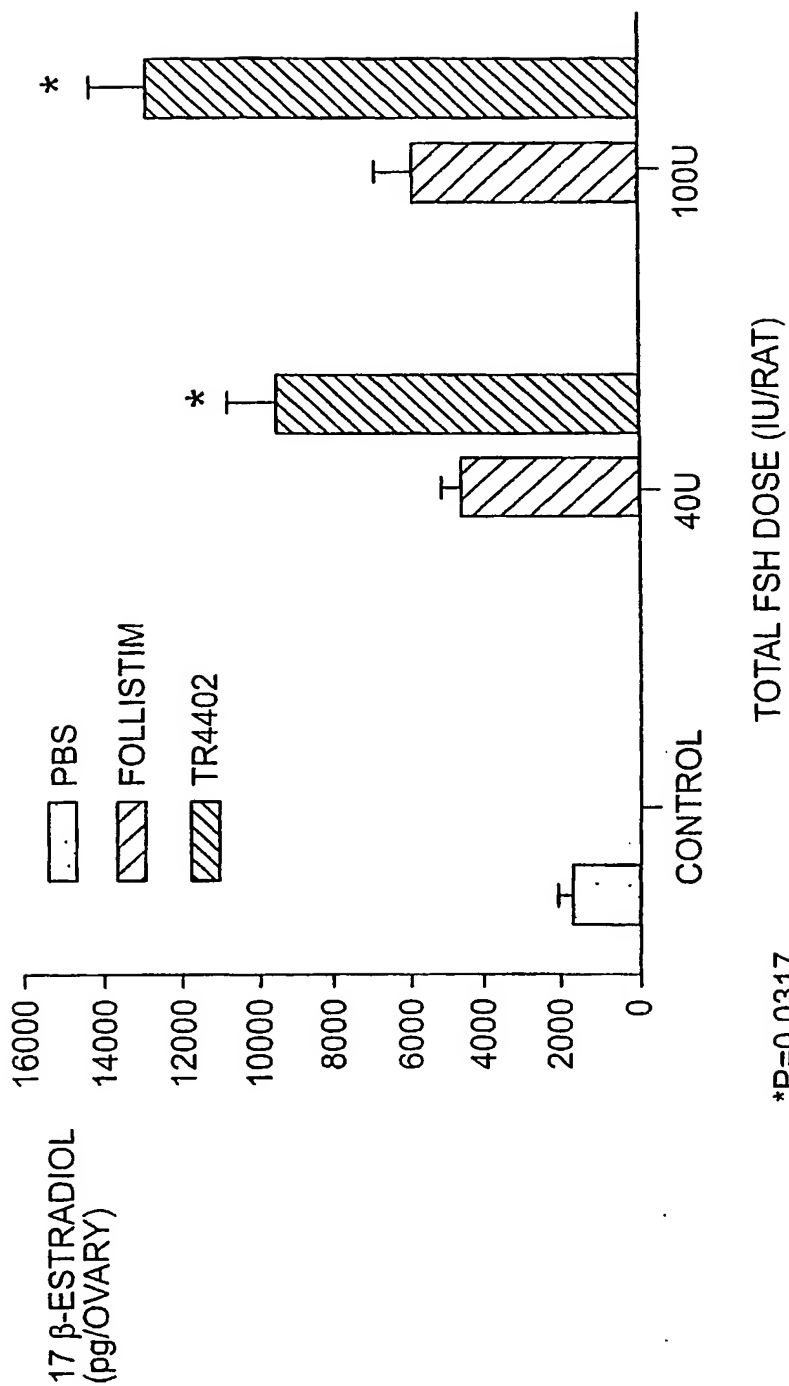
*CORRECTION OF OVARIAN WEIGHT BY BODY WEIGHT
CALCULATED BY: $100 \times \frac{\text{OVARIAN WEIGHT (mg)}}{\text{BODY WEIGHT (g)}}$

*TIME COURSE: 5 DAYS

FIG. 14D

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INTRAOVARIAN 17 β -ESTRADIOL FROM STEELMAN-POHLEY ASSAY



OVARIES WERE COLLECTED ON THE 4TH DAY AFTER THREE INJECTIONS.

FIG. 15

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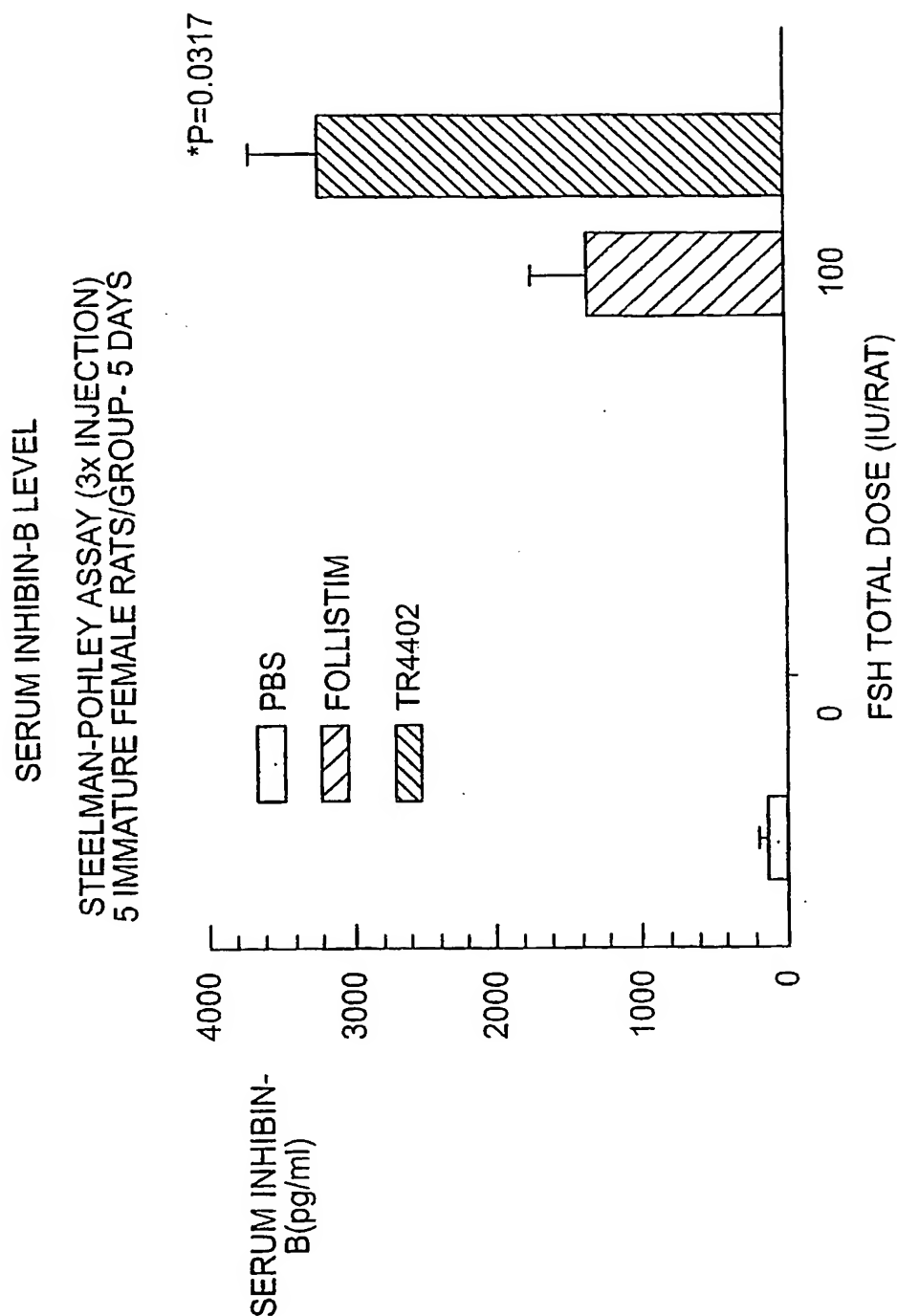


FIG. 16

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FSH CLEARANCE ASSAY

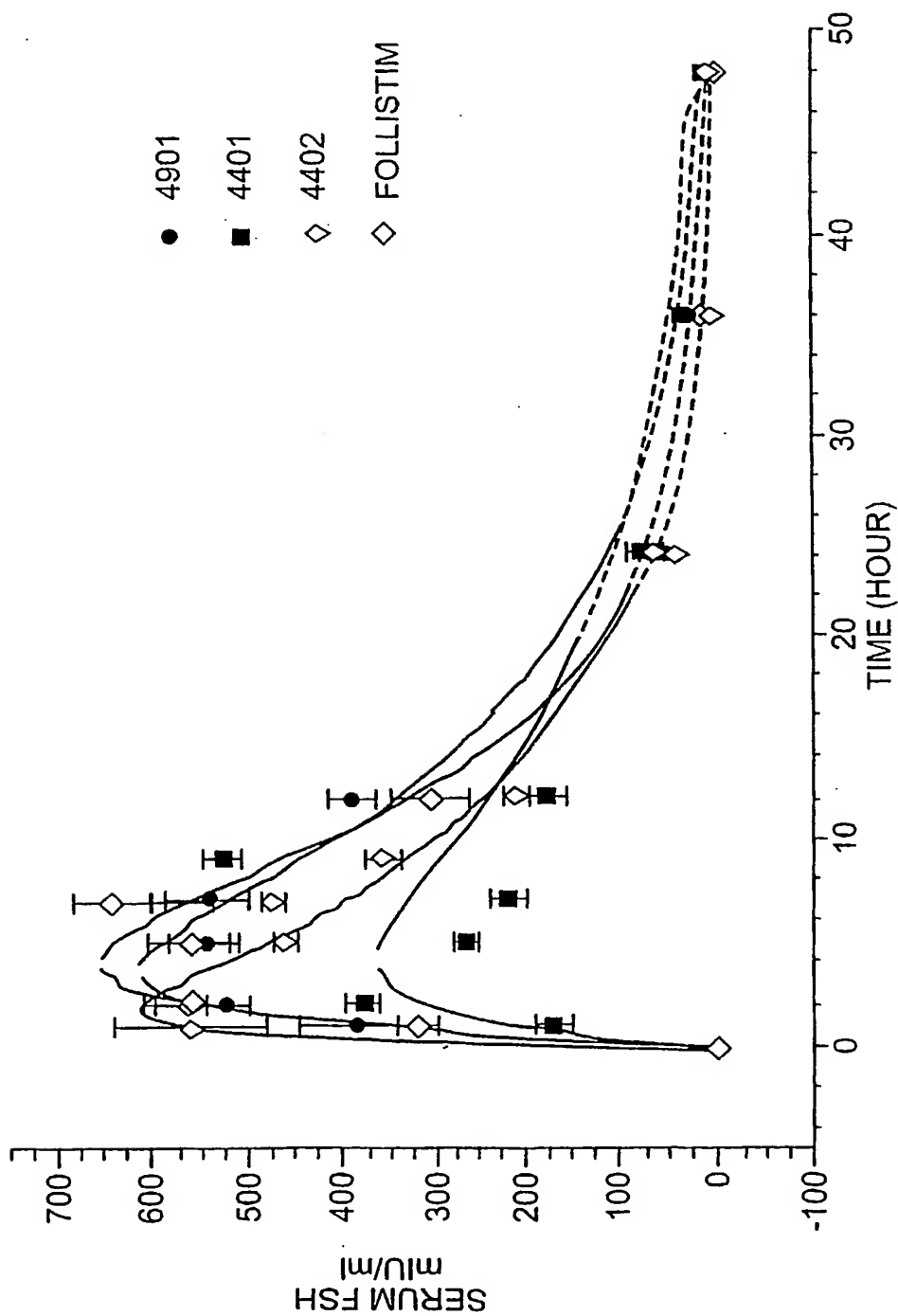


FIG. 17A

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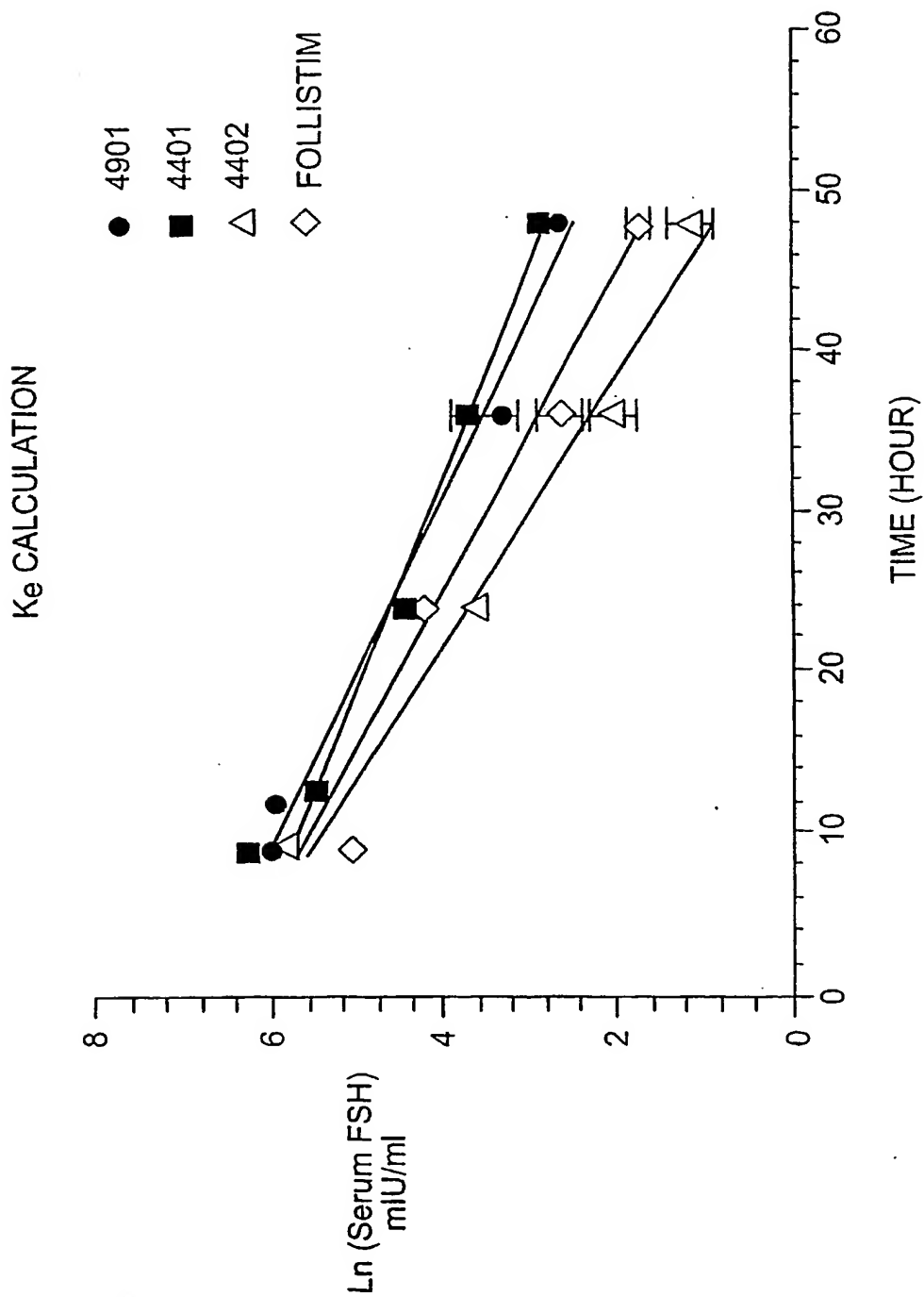


FIG. 17B

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LONGER ACTING TR4402-LA - MODIFIED, NOT BACK TO SCREENING

#1 N-TERMINAL EXTENSION (ANITV)

ANITVApdvqd cpeclqenp ffsqpgapil qcmgccfsra yptplrskkt mlvqkntse stccvaksyn
rvtvmggfkv enhtachcst cyyhks

#2 N-TERMINAL EXTENSION (ANITV) +E14R+Q20R+G73R+βE4R

ANITVApdvqd cpeclqRnp ffsRpgapil qcmgccfsra yptplrskkt mlvqkntse
stccvaksyn rvtvmgRfkv enhtachcst cyyhks

#3 N-TERMINAL EXTENSION (ANITVNIIV)

ANITVNIIVApdvqd cpeclqenp ffsqpgapil qcmgccfsra yptplrskkt mlvqkntse
stccvaksyn rvtvmggfkv enhtachcst cyyhks

#4 N-TERMINAL EXTENSION (ANITVNIIV) +E14R+Q20R+G73R+βE4R

ANITVNIIVApdvqd cpeclqRnp ffsRpgapil qcmgccfsra yptplrskkt mlvqkntse
stccvaksyn rvtvmgRfkv enhtachcst cyyhks

#5 V78N

ns cEltnitiai ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelvNetvr vpgcahhads
lytypNatqc hcgcKdsdst dctvrglgps ycsfgemke

#6 E4R + V78N

ns cRltnitiai ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelvNetvr vpgcahhads
lytypNatqc hcgcKdsdst dctvrglgps ycsfgemke

#7 Y58N

ns cEltnitiai ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelvNetvr vpgcahhads
lytypVatqc hcgcKdsdst dctvrglgps ycsfgemke

#8 E4R) + Y58N

ns cRltnitiai ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelvNetvr vpgcahhads
lytypVatqc hcgcKdsdst dctvrglgps ycsfgemke

FIG. 18

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cAMP STIMULATION ON hFSHR-CHO BY LA1-4402 & LA1-wt

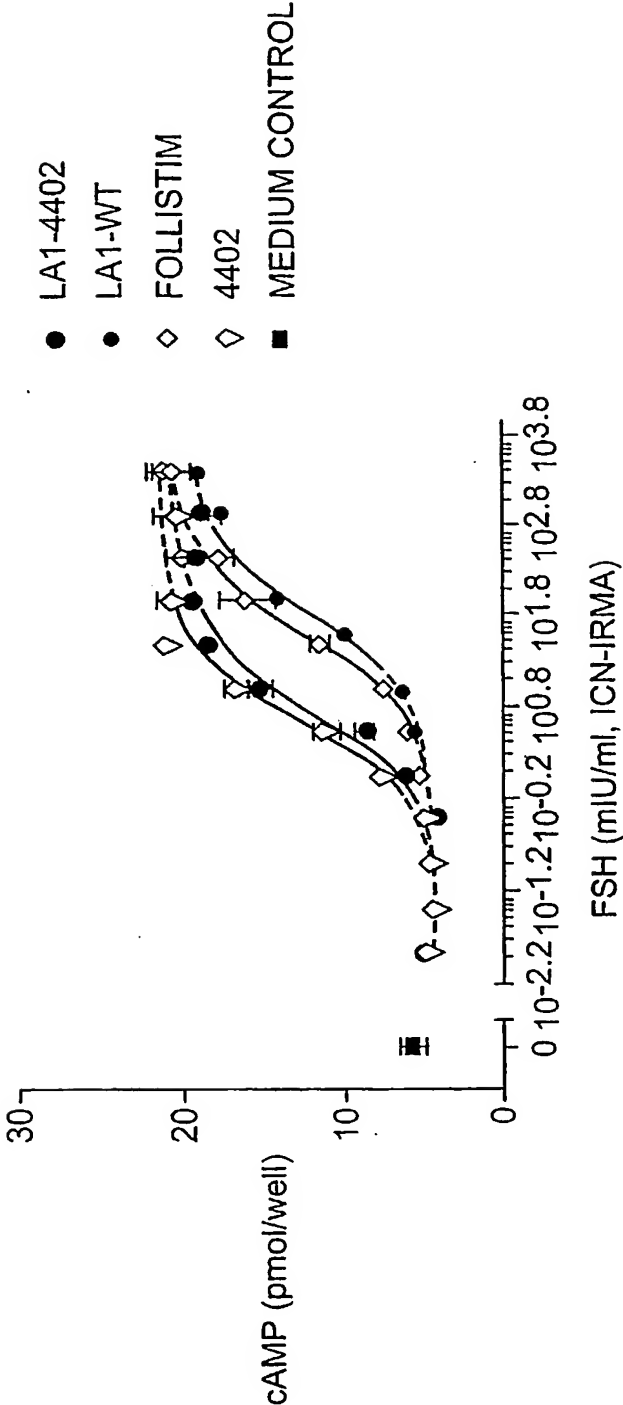


FIG. 19

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FSH GROUP FOLLOW-UP (PROOF OF CONCEPT)
4402-LA1 ANALOG WITH CORRECTED CLEARANCE OUT-
PERFORMS FOLLISTIM AT ALL DOSES
IN A GROUP OF "POOR RESPONDING" HYBRID MICE

OVULATION ASSAY IN IMMATURE HYBRID B6D2F1 MICE GENE LOGIC 1315-120

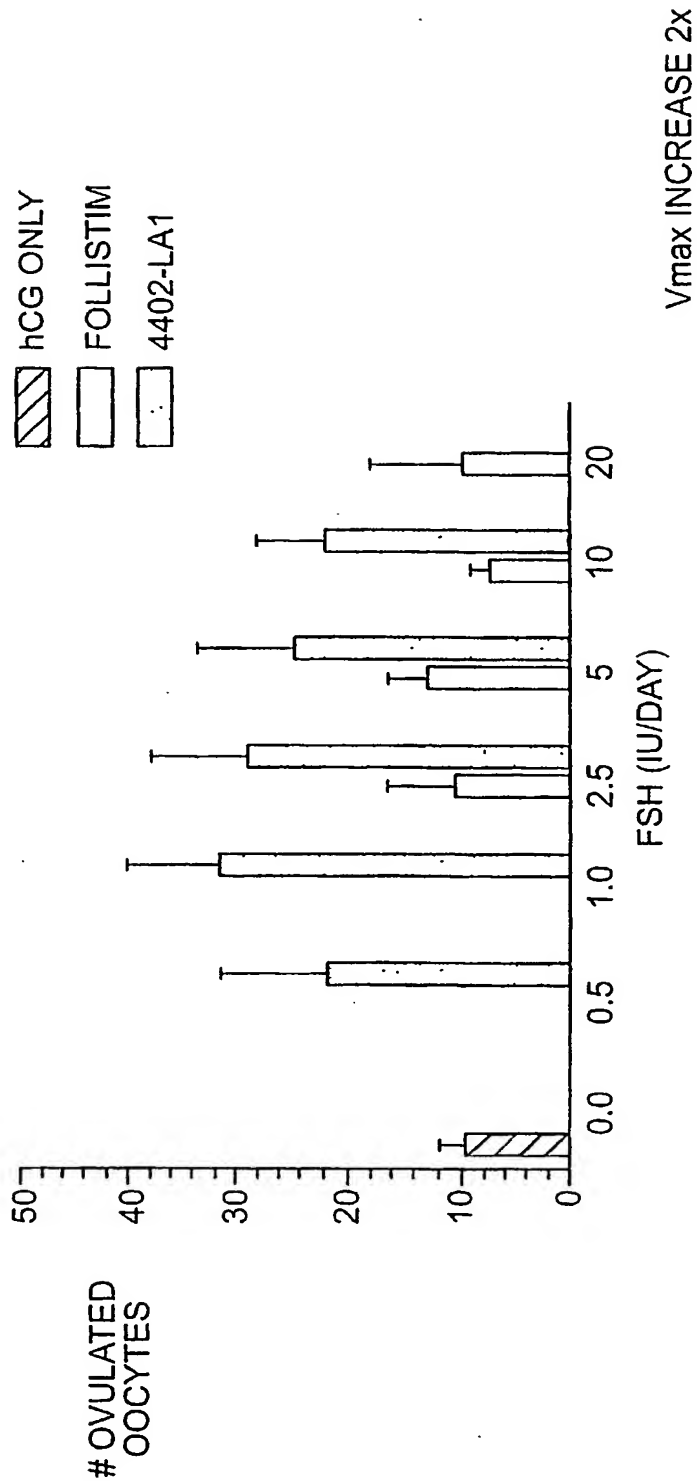
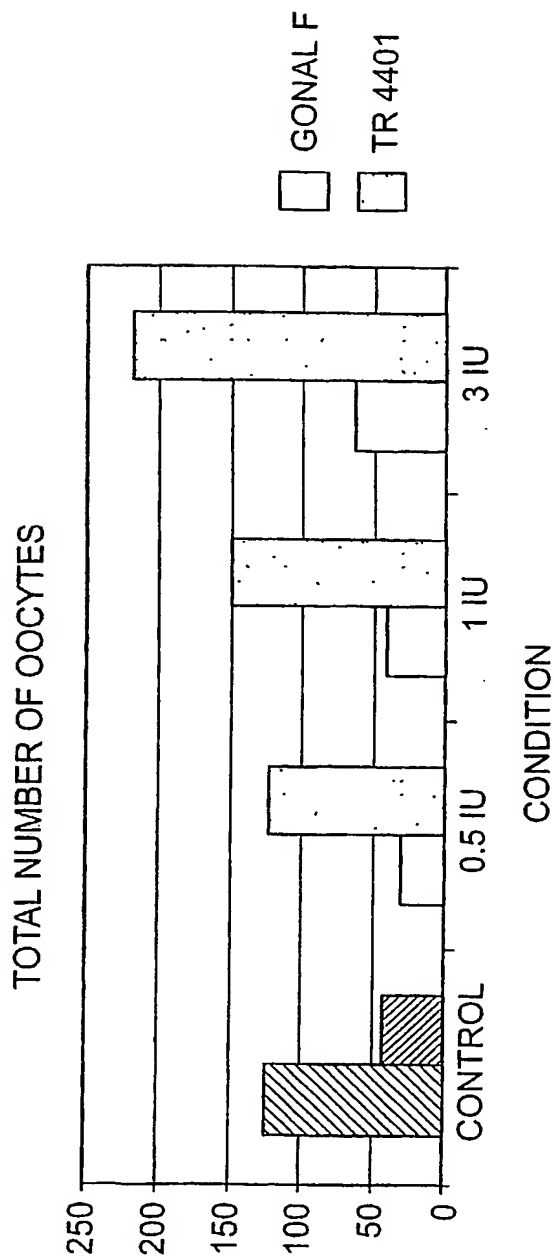


FIG. 20

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TOTAL NUMBER OF HEALTHY OOCYTES (FROM 3 MICE)
COUNTED AT SPERM WASHING



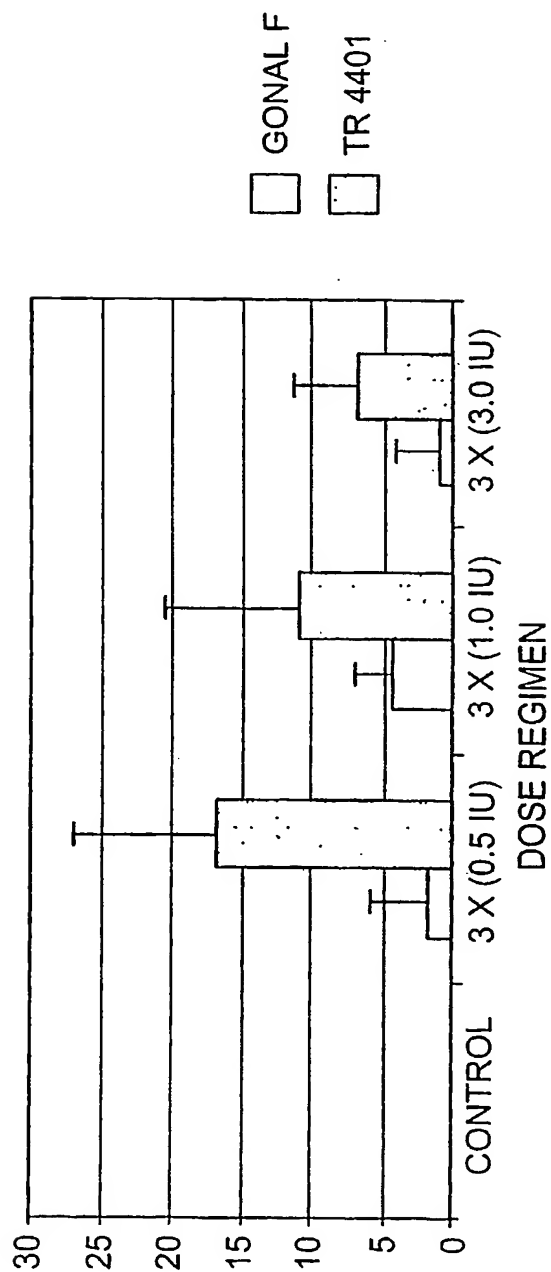
□ GONAL F □ TR_4401

CONTROL ▨ : POSITIVE CONTROL (2.5 IU FOLLIGON)
CONTROL ▩ : HCG ONLY

FIG. 21

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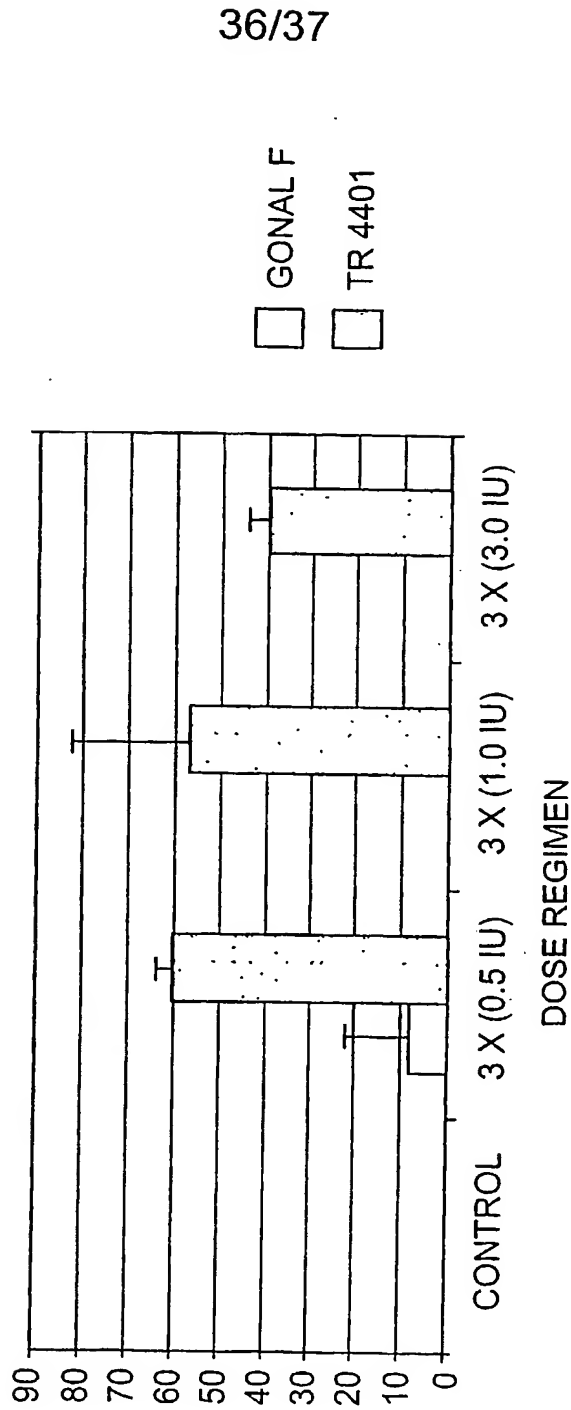
FERTILIZATION RATE EXPRESSED AS % OF 2-CELL/MOUSE



CONTROL: 3 X (1 IU hCG)
GONAL F AND TR 4401: 3 X (0.5, 1.0, 3 IU COMBINED WITH 1 IU hCG)
FOLLOWED ON DAY 3 BY 1 OVULATORY DOSE OF 15 IU hCG.

FIG. 22

BLASTOCYST FORMATION RATE EXPRESSED AS % OF BLASTOCYST / 2-CELL



CONTROL: 3 X (1 IU hCG)
 GONAL F AND TR 4401: 3 X (0.5, 1.0, 3 IU COMBINED WITH 1 IU hCG)
 FOLLOWED ON DAY 3 BY 1 OVULATORY DOSE OF 15 IU hCG.

FIG. 23

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TOTAL NUMBER OF EMBRYOS

NUMBER OF EMBRYOS

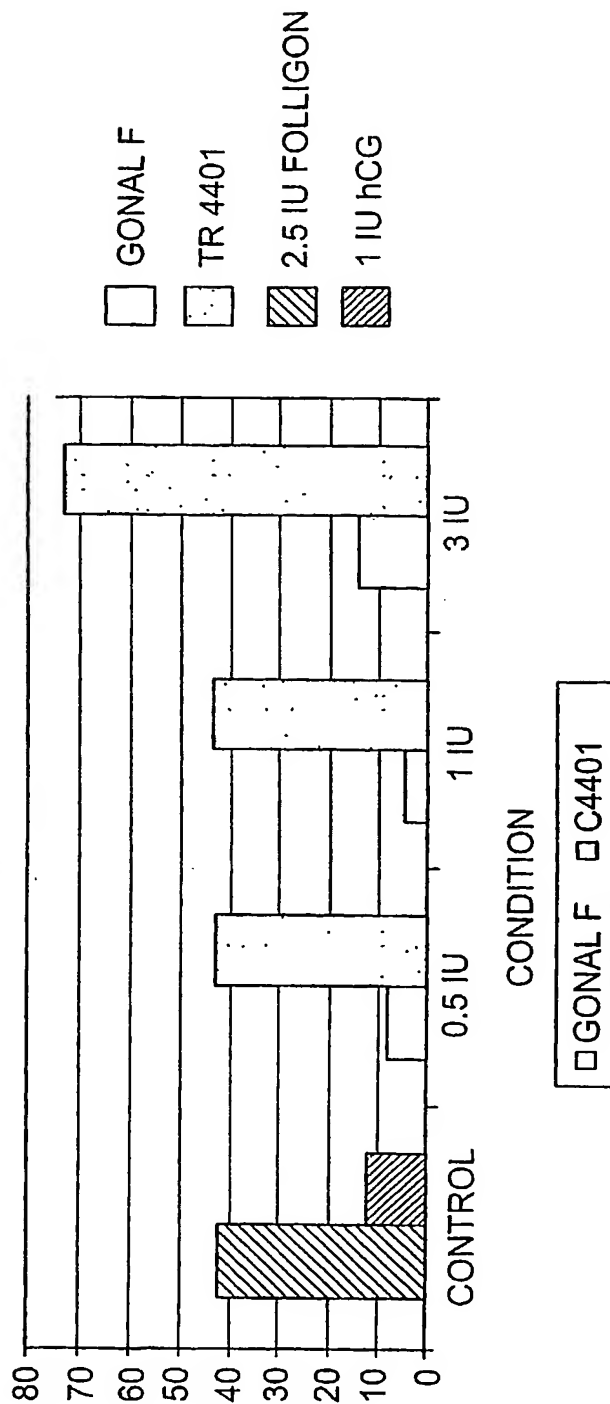


FIG. 24